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THE SHATTUCK LECTURE*

The Specificity and Reliability of Roentgenographic Diagnosis

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BOSTON

X-RAY films are not all black and white. Some parts may be black and others white, but there are many shades of gray in between. Similarly, the diagnoses from roentgenographic examinations are not all yes or no propositions. There are many shades of certainty in opinions and many degrees of reliability based on deductions. This essay is an attempt to estimate the accuracy and trustworthiness of diagnoses made primarily by the roentgenographic method. These estimates are based not only upon my own experience of thirty years with this method but also upon those of my colleagues both in roentgenology and in the associated specialties.

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The basic question that I asked my colleagues was, "What percentage of significant lesions capable of producing symptoms or apt to do harm to the patient can we demonstrate by the usual roentgen examination?" The corollary then was "Of the lesions demonstrated, how many can one identify etiologically or histologically with a fair degree of certainty?" The third phase of roentgenographic interpretation, which concerns the reporting of incidental lesions of usually minor clinical import such as old pleurisy, calcified tuberculosis, gastroptosis and hypertrophic spurs, is excluded from this survey.

These questions covering the major anatomic systems were submitted to and discussed with my colleagues, and our conclusions or averages are set forth below. It immediately became apparent that a wide divergence of opinion was present, particularly in the field of pulmonary disease. The answers seemed to be in line with optimism and conceit regarding one's individual prowess on the one hand, or with pessimism and humility on the other. Some were prone to forget their errors and the many indeterminate examinations, remembering their spectacular diagnoses, and others were just as apt to overlook the numerous easy and accurate diagnoses and reflect unduly on their failures and their mistakes. The answers were further qualified, particularly by the gastroenterologists, by the training and experience of the roentgenologists performing the examinations. This was met by the specification of "a good roentgenologist," since it is the possibilities of the method in good hands that we are trying to evaluate. Unfortunately, no x-ray machine yet available furnishes a diagnosis along with the film. Unfortunately, also, many patients and some referring physicians place entirely too much trust in the examination itself, disregarding the man who does it.

The orthopedists and the chest physicians both stressed the positive value of a completely negative roentgenographic examination, whereas the gastroenterologists were less impressed by its value. Both values depend, of course, upon the symptoms and physical findings. The ordinary pain in the back that causes so many patients to apply for examination has much less significance to the orthopedist if the x-ray examination is entirely negative. A negative gastrointestinal examination, however, in the face of an unexplained anemia or persistent blood in the stools may be not only valueless but actually harmful, if it prevents further search for a hidden ulcer or neoplasm. Rigler,[1, 2] in his articles on the possibilities and limitations of roentgenographic examination of the chest, has defined three factors that influence the results: the *time* of the start of the process, the *size* of the lesion and the *time relation* of symptoms or signs to the visibility of the lesion. I would add to this, in evaluating our accuracy of identification of lesions, the *frequency* of any given lesion, as modified by the age, sex and race of the patient, as well as its location, distribution and x-ray appearance. Richard Cabot, in the many years of conducting his famous case discussions (clinicopathological conferences), leaned heavily upon the mathematical probabilities in any given set of circumstances for his final diagnosis. When I first joined him in those exercises in 1922 he was of the opinion that "the diagnosis by x-ray is just about as apt to be wrong as it is to be right," but at the end of his career he came to depend more heavily upon roentgenographic examination, always qualifying it however with the question "Are you sure?" or "How sure can you

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be?" As roentgenologists I am sure that much of our accuracy depends upon the mathematical probabilities in a given case or set of circumstances. How certain can we be in our interpretations? How positive can we be with our observations and deductions? Our diagnoses are based on gross pathology (that is, disturbed morphology) in the great majority of cases — certainly, well over 90 per cent. Only a very small percentage is based on abnormal physiology, and the rest on congenital anomalies, probably less than 5 per cent each. The two major x-ray examinations based on physiologic tests are cholecystograms and intravenous urograms, both very important and useful diagnostic tools — the former highly reliable and accurate, and the latter best used only as a screening procedure and not as the ultimate diagnostic method. The congenital anomalies, such as extra ribs and malformed bones, are most frequently of no clinical significance but in certain locations, such as the heart, brain and gastrointestinal tract, may be extremely important.

The observations and deductions leading to a definitive diagnosis should be based on a careful analysis of all available evidence, and the question should be "What is going on?" not "What does that look like?" The latter is a mere memory technic and could be learned by a technician. The former is the rational approach, first seeing all the evidence recorded, next recognizing what each bit of evidence means, then adding it all up in terms of pathologic processes and finally correlating it with the history, physical findings and laboratory examinations — if available. Unfortunately, the x-ray examination is often performed before many of these are available. The wise roentgenologist may withhold or qualify his final opinion, or indicate what test is necessary to confirm his suspicions. In the final analysis, there is no substitute for experience and judgment. Some of us are too conservative, influenced too much by our failures and errors, and others are too positive. It would be ideal if we could establish a definite set of criteria for analysis of each examination — criteria so detailed and exact that one would merely have to add them up on a comptometer and arrive at a mathematically exact diagnosis. Unfortunately, we have no such criteria, for diseases of the human organism do not always reproduce the same pattern. Our decisions, therefore, and our accuracy in diagnosis must continue to be based upon our own experiences, although influenced, it is true, by tribal beliefs and often by inheritances from our own teachers or preceptors. These decisions (conclusions) are apt to be least dogmatic when one is surrounded and constantly checked by specialists of equal or greater ability. (At this point I should like to pay my sincere homage and respect to Drs. Christian, Cushing and Wolbach, a magnificent trio of "checker-uppers.")

In offering a conclusion or a deduction or an impression after describing the facts obtained from x-ray examination, it is always helpful to indicate the certainty of that deduction. This certainty may grade all the way from white to black, including the intervening shades of gray, but for practical purposes can be divided into the following seven groups:

Some conclusions from roentgenographic examination can be classed as indubitable or absolutely certain, such as fractures, dislocations, pneumothorax, pleural fluid, gallstones and many others.

Only slightly below in certainty are those which may be classed as "highly probable" or "in all probability," such as renal and vesical calculi, metastases, advanced carcinoma, many cases of pulmonary tuberculosis, ulcer, pituitary tumors and a host of other conditions.

Next in the degree of sureness would be the statement "probably," indicating possible doubt, but evidence definitely in favor of one diagnosis, such as pulmonary infarct or consolidation, primary lung tumor, early carcinoma and metabolic bone disease.

A large group of cases can only be reported as "possibly —," "could be —," or "unable to differentiate between — — —." This would include atypical miliary diseases of the lung, unusual bone conditions, many renal diseases, obstructive lesions in the colon or small bowel and many others. This group includes numerous cases in which the lesion is located — for example, by ventriculography, enema or pyelogram — but with insufficient evidence to identify it as tumor, abscess, hemorrhage or anomaly.

There are many minor changes in structure or function that should be reported, but their importance should also be assayed for the benefit of the referring physician. If justified by the evidence these may be reported as "probably of no clinical significance." This includes many congenital anomalies, pleural scars, calcified lymph nodes, obsolete minimal pulmonary changes in elderly people, calcification of the aortic arch and hypertrophic spurs in older patients. A useful statement in this group is "not unusual for this age."

"Normal" indicates a completely negative examination and no explanation for symptoms or signs. The value of such a negative report varies widely, but it helps to rule out the more serious conditions in most cases of headache, backache, fever, cough and abdominal discomfort.

The most serious and distressing group is the one in which the roentgenographic examination is completely negative in the face of distressing symptoms or positive signs of disease. This is the usual result in most cases of angina, a few gastric hemorrhages, many patients with positive guaiac tests on the stool and many cases of brain tumor (plain films only).

One further group, which I hesitate to reveal, is what one of my former assistants called "Sos-

man's psychological side-step." In this rare group of cases there may be a hint or a suggestion of a disease that could explain the patient's symptoms, but no real evidence to support it. However, by naming the disease, if only to deny it, one brings the condition to the physician's attention, and appropriate tests may confirm or exclude it. Such statements as "I do not believe these are metastases from prostatic cancer" or "not sufficient to justify a diagnosis of acoustic neurinoma" may lead eventually to a correct diagnosis without undue alarm and without discredit if they are negative.

A summary of these groups numerically is attempted under the individual anatomic systems. As a whole, well over 50 per cent of examinations in these days of widespread "routine" examinations are completely negative, or demonstrate no significant lesions. This is particularly true, of course, in the routine screening of the chest so widely employed to the great benefit of all concerned. Screening technics, however, are not included in these estimates.

The Chest

Considering the chest, and pulmonary diseases in particular, we find at once a wide divergence of opinion. In a study to determine the accuracy of various screening methods Birkelo and his committee[3] found that there was less variation in the different technics employed than in the individual opinions about what was significant. Not only did individual readers vary among themselves but also the same person did not select the same cases on subsequent rereading of the same series of chest films. This report created a mild sensation, particularly in the ranks of roentgenologists, but it was amply confirmed by Garland[4] and others. Rigler's[1,2] careful analyses of the factors leading to a correct diagnosis of intrapulmonary lesions, particularly neoplasms, further amplified the situation. All three reports, by three outstanding groups of roentgenologists and chest physicians, indicate, however, that roentgenology has come of age, in that all three present healthy self-criticism and constructive suggestions for improvement. It became evident from studying these reports, and similar ones, that the findings in chest roentgenograms can be divided readily into three groups. The largest one is the normal group, with no evidence of any disease or abnormality; the next is the frankly abnormal group; and the third is the small group of borderline cases in which questionable changes were thought to be significant by some readers (the pessimistic group) or of no probable significance by the other group (the optimists). Out of this grew the suggestion by Garland that all survey films should be either read independently by two separate physicians or read twice by the same person, first from a pessimistic viewpoint and then rechecked from the optimistic viewpoint.

Turning to the clinic, where the majority of patients are either ill or have some symptoms of illness, we find an astonishing agreement on the ability of the roentgenographic examination to demonstrate significant or symptom-producing lesions in well over 95 per cent of cases. Just as astonishing, however, is the wide divergence of opinion about how many of the lesions demonstrated can be identified. Some think it is as low as 10 per cent, and others as high as 90 per cent. Without going into minute details, and excluding the common colds and the ubiquitous "chronic bronchitis" of New England, my own opinion is that the pulmonary lesions can be identified with a high degree of certainty in 75 to 80 per cent of cases. It must be acknowledged at once that the final diagnosis in pulmonary tuberculosis, for example, rests upon the demonstration of the tubercle bacillus just as that of carcinoma of the lung depends upon histologic proof. The point is that a reasonable certainty of predicted diagnoses can be obtained in about four fifths of the cases with only the usual x-ray examination such as posteroanterior, oblique or lateral films. This accuracy can be increased perhaps by 5 per cent if special roentgenographic technics are added, such as bronchography, body-section roentgenography, careful fluoroscopy, films on inspiration and expiration, overexposed Bucky films, spot films, lateral decubitus films and all the other special examinations including angiography. The dividends from repeated or special examinations are not as great in the field of lung disease as they are in the gastrointestinal tract, which is discussed below. Time, however, is an important ally, and serial examinations over a period of days, weeks or months often clarify the diagnosis by the natural evolution of the disease. We are not counting on this factor in our analysis, however, for a delay in diagnosis too often allows an early malignant lesion to progress beyond the operable stage.

The day has passed, I believe, when we can be content (as we were told to be in 1920) with merely describing the lesion and leaving the diagnosis to the referring physician. We as roentgenologists must consider not only the x-ray appearances but also all other available facts, and render as definite an opinion as the circumstances may justify. Only by so doing can we sharpen our acuity, increase our experience and judgment and be of greater help to our patients and to our referring physicians. In all our work we should try to live up to Sollmann's[5] criteria of scientific observations:

> Scientific observation is not merely the recording of facts; a photographic plate records facts but does not make observations. True observation requires objective accuracy, but it also demands selective discrimination.*

*For details in individual lesions as well as the relation between the onset of disease, symptoms and positive roentgenographic findings, the reader is referred to Rigler's Pancoast Lecture.[2] For the relation between the *demonstration* of a pulmonary lesion and its *perception* by the roentgenologist, the articles by Birkelo et al.[3] and Garland[4] are recommended.

It is difficult to assay our accuracy in the diagnosis of heart disease, but roentgenographic examination, particularly fluoroscopy, can be of considerable help. Our contributions in cardiology are considerably less important than in the field of pulmonary diseases, where roentgenographic examination is essential.

The Gastrointestinal Tract

Gastrointestinal examinations, properly done, require the greatest time, skill, patience, effort and judgment of any roentgenographic examinations, with the sole exception of the highly specialized fields. The diagnostic dividends, moreover, are in direct proportion to the training and skill of the examiner. The ideal method is a combination of careful fluoroscopy, including spot films, with routine radiographs and special positions as indicated either by the history or by the examination. It is also the most dangerous type of work for the radiologist (with the exception of radium therapy) so that the amount of such work done by any person each day should be strictly limited according to the exposure received. Up to the present time routine screening procedures have not proved very useful or valuable, but the widespread dependence upon the method has placed it almost on a "routine" basis. Physical examination of the alimentary tract, aside from palpatory demonstration of abnormal masses and localized tenderness, is almost entirely dependent upon inspection by proctoscope or gastroscope, digital examination of the rectum (too often omitted) and the roentgenographic method. In no other anatomic field is the physician or surgeon so heavily dependent upon the roentgenographic method for so many of his decisions. However, as is also true in the field of pulmonary disease, the highest accuracy and the greatest benefit to the patient accrue when the physician, surgeon or gastroenterologist works closely with the roentgenologist, sharing their facts, ideas and suspicions as well as their experience and judgment.

The major problem in gastrointestinal roentgenology is the demonstration or detection of the lesion. Once it is clearly demonstrated, the identification is easier and correspondingly more precise. This is largely due to the fact that there are fewer choices — that is, fewer types of lesions recognizable and demonstrable — than in pulmonary diseases. The great majority of lesions in the upper portion of the tract are either ulcer or cancer, with anomalies such as duodenal diverticula in third place. In the colon the most common lesions are diverticula and cancer, with the infections and anomalies making up most of the small residue. The value of a negative examination in the presence of symptoms, or of signs such as occult bleeding, is considerably less than in the chest. Such conditions call for a re-examination and sometimes repeated examinations using all the special technics available.

We believe that we are able to demonstrate 80 to 85 per cent of all significant lesions in the gastrointestinal tract and, having perceived them, are able to identify them correctly in about 90 per cent of cases. The lesions we miss most frequently and most easily are small polyps in the colon, superficial erosions in the stomach and some peptic ulcers, particularly those high in the stomachs of obese persons. Obese patients may be very difficult to examine satisfactorily, since the stomach and duodenal bulb may both be above the costal margin so that we cannot compress them manually or do adequate spot-film examinations. Obesity is a definite hazard to life, since it interferes with early and accurate roentgenographic diagnoses.

There is some argument between gastroenterologists and roentgenologists about whether gastric or duodenal ulcers are more frequently overlooked. Duodenal ulcers are ten times as common as gastric ulcers in our clinic, so that numerically it is probable that we overlook more duodenal than gastric ulcers. However, in percentage, I believe that we miss more of the gastric ulcers, especially in the patient who is hard to examine. Fortunately, the gastroscopist can visualize some of those we miss, and can identify gastritis and superficial ulcers, but he cannot possibly examine as many patients as we do, so that his clientele is a highly selected one. Unfortunately, he obtains no permanent record of what he has seen and we must rely upon his visual impressions.

In a previous study[6] of 1649 consecutive gastrointestinal examinations, 354 peptic ulcers were demonstrated, mostly duodenal in location. Of the 8 errors known to have been made in the stomach group, 6 were incorrect differentiation between ulcer and carcinoma. We do not know how many lesions were missed entirely. Many of the gastric ulcers disappeared entirely under appropriate therapy, but it was extremely rare for the deformity of a duodenal ulcer to disappear under any conditions. Only a few (1 or 2 per cent) of the deformed duodenal bulbs returned to normal even if the patient was free of symptoms. Those which did return to normal were usually in young patients with a short history of ulcer. This suggests that the deformity is at first due to spasm but in the cases of longer duration is due to actual scar formation. The *activity* of a duodenal ulcer can be inferred by roentgenographic examination only in the cases in which a definite crater is demonstrated. This is possible in only 10 to 15 per cent of the deformed duodenal bulbs (and occasionally in a bulb that fills normally), so that we must miss many shallow ulcers in the deformed bulb. However, the case is recognized as one of "chronic duodenal ulcer," and in my experience neither the degree of deformity nor the absence of a crater has any constant correlation with the patient's symptoms.

The most difficult problem in the gastrointestinal tract is the demonstration of a gastrojejunal ulcer.

The disturbed anatomy and the abnormal mucosal folds present after operation both increase the difficulty of demonstrating an ulcer crater. We must miss the majority of marginal ulcers.

The Osseous System

The third large anatomic system that is more easily studied by roentgenographic methods is the bony skeleton. It was one of the first to be examined by the new method of Roentgen, and many volumes have been written about its anomalies, diseases, injuries and tumors. It is difficult accurately to assay the specificity and reliability of x-ray diagnoses in this system, for the manifestations of disease are so many and varied and the borderlines are so often ill defined. In general we may say, however, that the demonstration of lesions in the bones is easier than their identification, as it was in the lungs. Most of the significant lesions of the skeleton are demonstrable by roentgenographic examination, the exceptions being early osteomyelitis (which has almost disappeared since the advent of chemotherapy and antibiotics) and early metastatic cancer, which is becoming more of a problem in the aging population. At least half the diagnostic problems in this field have to do with trauma, and we are able to demonstrate fractures or dislocations in well over 95 per cent of cases. Including fractures, we are able to demonstrate over 90 per cent of significant lesions of the skeleton and, having shown them, can identify them in about 90 per cent of cases. These excellent figures, however, do not hold for all subdivisions of the field. Primary bone tumors are relatively rare, fortunately, but when significant, or when producing symptoms, can be demonstrated in almost 100 per cent of cases. Their identification as tumors is also high, probably 90 per cent, but opinions about their histologic type, or even about their benignancy or malignancy, are definitely lower in accuracy, probably nearer 80 per cent. Metabolic disease of bone is even rarer, and must be fairly well advanced before we can recognize it roentgenologically except in the growing bones of infants and children, where changes are seen early, and may be pathognomonic even before the onset of symptoms. Metastatic cancer in bone is usually demonstrated and recognized readily, but in the early stages, even when producing symptoms, may be undemonstrable. For that reason it is always wise, in a patient with known cancer and with a constant aching pain in the spine, for example, to start treatment for metastatic tumor even if the x-ray examination is negative.

The value of a negative examination in patients with symptoms referred to the osseous system is also high, since it rules out many if not most of the serious conditions. In the host of patients who come to us with a pain in the back, we are able to demonstrate significant changes in only 10 per cent. Of course, there are many minor changes, and these may achieve major importance if one is a chiropractor or an osteopath, but those changes are still present when the symptoms disappear. Each specialty has its own list of causes of pain in the back, and each its own method of treatment. The orthopedist attributes it to faulty posture or ill fitted shoes. The neurosurgeon thinks it is a ruptured disk. The gynecologist knows it can be due to malposition of the uterus, the internist blames constipation or infected teeth, the psychiatrist finds an Oedipus complex to explain it, and so it goes. Actually, pain in the back is a *dolor in neckibus* to the roentgenologist, since many patients feel frustrated and cheated when we report the examination as negative. We hasten to explain that they should feel comforted because we could find nothing serious, but they go away still doubtful and many end up with the osteopath or Christian Scientist, to the detriment of medicine. Some roentgenologists are even driven to reporting in detail all the minor variations and unimportant abnormalities, hoping by so doing to retain their ethical and social standing in their community, where so many of their friends suffer from pain in the back.

The Genitourinary Tract

Roentgenographic examination is used in about 90 per cent of all patients seen by the urologic surgeon. In combination with the cystoscope and the microscope a positive diagnosis can be made in nearly all significant lesions of the urinary tract. Roentgenography can be used in either of two ways: by injection of opaque material through a catheter, or by intravenous injection of suitable organic iodides, which are excreted by the kidneys as a component part of the urine. Thus, we have available a passive demonstration of morphology or a rough functional test of excretory ability. The latter does not usually give as good anatomic detail as the former, but its particular field of usefulness is as a screening procedure, selecting certain patients for more thorough investigation. Again, the relative frequency of some lesions and the small variety of total lesions favor easy demonstration and ready identification by the roentgenographic method. A high percentage (90) of calculi in the urinary tract is opaque to the roentgen ray. Primary tumors large enough to cause symptoms nearly always cause gross recognizable changes in the morphology of the renal pelvis, ureter or bladder, but early tumors of the renal pelvis and urinary bladder may cause bleeding while still quite small and may be entirely overlooked by urograms, pyelograms or cystograms. Injuries to the kidney are relatively rare. Gross damage is recognizable by pyelography only when the renal pelvis or calyxes are ruptured. Infections of the kidney rarely cause gross changes in morphology except in the chronic stage or when tuberculosis is the causative agent. Enlargement or distortion of the renal shadow may, however, be the clue that leads to the identification of tumor, injury or infection.

In summary, the roentgenographic examination of patients referred by a urologic surgeon demonstrates the lesion in about 90 per cent of all cases, and identifies it in an equal percentage. If we were to include the various forms of nephritis, many of them not seen by the urologist, the incidence of demonstrable lesions would be considerably lower, nearer 70 per cent.

The Skull

Lesions of the cranial vault not originating within the skull come more properly under the osseous system. We shall consider in this paper only the intracranial lesions as seen in a hospital with an active neurosurgical service. In the average hospital, skull roentgenograms are made most commonly either for fracture or for nonspecific symptoms such as headache, and occasionally as a part of a skeletal survey for metastases or metabolic bone disease. In 1931, the last full year of Dr. Harvey Cushing's service at our hospital, we kept a daily record of all skull examinations,[7] a consecutive record of 1219 examinations of 939 patients, with a follow-up study, particularly, of verified intracranial tumors, 175 in number. In addition there were 17 calcified or destructive tumors unverified, and 9 pituitary adenomas not surgically verified, a total of 201 tumors. By ordinary x-ray examination we were able to obtain enough evidence to localize the tumor in 47 per cent of the cases, and to predict its histologic type in 26 per cent of all tumors, or 52 per cent of those demonstrated or localized. From an analysis of the histories it seemed evident that the roentgenographic examination definitely aided the diagnosis in 23 per cent of the cases, made the diagnosis alone in 7 per cent and gave misleading signs in 4 per cent. When ventriculograms were employed, 116 being done that year, 59 out of 62 tumors subsequently verified were correctly located — 95 per cent. Two of the 3 errors were thought to be due to incomplete filling of the ventricles, a circumstance beyond our control, and the third error was made by an observer inexperienced with the method. This tends to bear out Dandy's statement that almost every intracranial neoplasm large enough to cause symptoms can be located by ventriculography. If we should add cerebral angiography, which is being employed more widely these days, particularly for vascular abnormalities and aneurysms, we can more nearly approach a perfect score in the diagnosis of intracranial lesions.

In summary, we can say that "routine" roentgenographic examination gives localizing signs in almost half the intracranial tumors, and identifying evidence in a fourth. If the special procedures of ventriculography and angiography are added, well over 95 per cent of the tumors and vascular lesions can be demonstrated, but still not more than a third can be identified with any degree of certainty.

The opaque materials used in the examination of the spinal cord (Lipiodol or Pantopaque) have added greatly to our accuracy in this field, but there is still room for considerable improvement.

Gall Bladder

The final system for analysis of specificity and reliability in diagnosis is the biliary system. Originally, we were limited to the demonstration of "positive" gallstones, comprising only about 20 per cent of all gallstones. Since Graham's announcement of the selective excretion of tetrabromphenolphthalein by the liver and its concentration by the gall bladder, we have tremendously improved our diagnostic accuracy. In a previous paper before this society[8] our results with cholecystography were reported in detail, and I shall but summarize them here.

Cholecystography is one of the most accurate of medical diagnostic tests, combining as it does both physiologic and morphologic information with a minimum of choice in diagnosis. The accuracy of this test depends heavily on good technic, and less on experience and judgment. By minimum of choice, I mean that there are only three major results possible from cholecystography — no gall-bladder shadow demonstrable; a normal gall-bladder shadow is seen, with no evidence of calculi; calculi are visualized, either as "negative" areas in the gall-bladder shadow, or as "positive" (dense) shadows, which may occur either with or without visualization of the gall bladder. A peculiar paradox exists in this field of our work in that our accuracy in identifying disease exceeds in the total cases our demonstration of the disease. This is because nonvisualization of the gall bladder is almost as accurate an index of disease as the demonstration of calculi. If no gall-bladder shadow can be demonstrated, and if all related factors are checked and found to be correct, the gall bladder will be found to be grossly diseased in over 95 per cent of cases. If calculi are demonstrated, the accuracy should closely approach 100 per cent, depending only upon how certain one is of his observations. Our errors in this field are largely due to errors in technic, and only a few are errors in judgment, usually the interpretation of gas bubbles over the gall-bladder shadow as calculi or vice versa.

With the advent of Priodax (beta-[4-hydroxy-3,5-diiodo-phenyl]- alpha-phenylproprionic acid) the intravenous method of administration has been abandoned in favor of the oral method, with the consequent simplification of the test and universal employment of the method. It is still wise to repeat the test with a double dose of Priodax if the first examination results in nonvisualization of the gall bladder. The test will still fail in the presence of obstructive jaundice, of course, and in patients with obstructive lesions at or above the pylorus, since the Priodax must reach the small intestine to be absorbed.

Summary and Conclusions

After more than fifty years of use in diagnostic medicine, the roentgenographic method of physical

examination has become fairly well stabilized at a high level of accuracy. This is now the most widely used of all consultative methods. An analysis of the specificity and reliability of x-ray diagnosis by well trained and competent clinical roentgenologists reveals that we are able to demonstrate and then, of those perceived, to identify significant lesions in the various anatomic systems as follows:

System	Demonstrate %	Identify %
Lungs	95	75 to 80
Gastrointestinal tract	80 to 85	90
Bones	90	95
Genitourinary tract	90	90
Brain {Plain films	47	50
Brain {Special technics	98	30
Gall bladder	80	99*

*Of all cases.

In addition a negative examination, or failure to demonstrate a significant lesion as the cause of symptoms or signs, is also often of positive value, since it excludes many or all of the usual causes of such symptoms. No arbitrary value or accuracy can be assigned to such negative results, which are beginning to form the major part of our work as our combined efforts progress more and more toward preventive rather than curative medicine.

George Cheyne Shattuck, M.D. (1783-1854), the founder of this lecture and his grandson, Dr. George Brune Shattuck, who gave the first annual Shattuck Lecture in 1890, would both be astounded could they but see the high level of scientific medicine being practiced everywhere in this country today. Nothing could astonish them more, I am sure, than the daily widespread useful application of Professor Roentgen's invisible rays.

The lecture was illustrated by lantern slides exemplifying the difficulty of identifying certain conditions.

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ACUTE ADRENAL INSUFFICIENCY

Its Treatment and Prevention

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Addisonian crisis is a major medical emergency, like diabetic acidosis, which requires the constant supervision of the physician for a period of days. During the past ten years knowledge of the physiologic basis of adrenal insufficiency has increased; concomitantly, potent specific hormone preparations have become available. It is important for the clinician to be able to use this knowledge and these preparations with maximum efficiency. Delayed, inadequate or too enthusiastic therapy may result in a death that could have been avoided by prompt, intelligent use of the available tools of treatment.

There is a need for a definite plan of management of the phase of crisis to save time, to avoid confusion, to give the physician more self-confidence when faced with his first cases and to facilitate the analysis of results. Because successful therapy of acute adrenal insufficiency is relatively new, and the disease relatively rare, the literature on the subject is scanty. The plans of treatment discussed below are based on a survey of the literature and personal experience with 22 cases at the Massachusetts General Hospital from 1946 through 1949.

This presentation is divided into three sections: the therapeutic armamentarium, the treatment of three different forms of Addisonian crisis and the prevention of crises in susceptible patients.

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Therapeutic Armamentarium

Intravenous Injection of Fluids

The most useful single solution is 5 per cent dextrose in isotonic saline solution, which contains the two substances that are most needed by the patient. Stronger dextrose solutions are recommended under certain circumstances, as pointed out below.

Plasma and concentrated human albumin are useful in severe crises that do not respond to other measures. Whole blood should be reserved for cases complicated by actual blood loss, as in crises associated with severe trauma or surgical operation.

Desoxycorticosterone Acetate

This synthetic steroid has a potent sodium-retaining and potassium-losing effect, but probably no effect on carbohydrate metabolism. There are at present three equally good drugs on the market — Cortate, Doca and Percorten — 1 cc. of which contains 5 mg. of the desoxycorticosterone acetate in oil. This preparation costs about $0.90 per cubic centimeter or $0.18 per milligram. Toxic reactions attributed to it are headache, edema (pulmonary and peripheral), high blood pressure, heart failure, low potassium syndrome, tendon contractures and sudden death.

Adrenocortical Extracts

These are of two general types — aqueous and oily solutions. There are a number of aqueous preparations of similar potency. The cost is about $0.50 per cubic centimeter. Constitutional reactions from sensitivity or overdosage in amounts up to 200 cc. daily have not been reported. Local irritation at the site of injection is fairly frequent but not serious.

The oily extract is from hog adrenal glands, in contrast to the aqueous, which is bovine in origin. The preparation is called Lipo-Adrenal cortex, and costs about $5 per cubic centimeter. General reactions of mild degree (myalgia and fever) have been reported but are thought to be due to an impurity in the oil. As with the aqueous preparation, no symptoms of overdosage have been reported.

The approximate comparative strengths of the various preparations and the time required for their action[1, 2] are shown in Table 1.

Table 1. *Comparative Strengths and Time of Action of Various Adrenocortical Preparations.*

Preparation	Electrolyte Effect	Carbohydrate Effect	Time of Maximum Effect After Intramuscular Administration	Duration of Action After Intramuscular Administration
		cc.	*hr.*	*hr.*
Lipo-Adrenal cortex	1 cc.	1	1–4*	10–12
Aqueous adrenal extract	10 cc.	10–20	1–4*	6–8
Desoxycorticosterone acetate	1–2 mg.	—	12	24

*Depending on time of carbohydrate intake.

For therapy, the following conclusions appear justifiable:

Aqueous adrenal extract, which can be given intravenously, is more desirable during the early stage of the crisis, when intramuscular absorption is slow because of impaired circulation; Lipo-Adrenal cortex is better suited to the later stages.

Desoxycorticosterone should be used with caution because of the serious consequences of overdosage, whereas the various whole-gland extracts are safe in large doses.

Antibiotics

These agents have a prominent place in the therapy because infection is such a common precipitating factor. Since there may be fever without infection, and infection without fever, it is advisable to use the antibiotics routinely. At present, penicillin is the drug of choice because of its wide range of antibacterial effectiveness and ease of administration and because it is well tolerated.

Three Forms of Acute Adrenal Insufficiency and Their Treatment

From the standpoint of therapy it is convenient to divide the cases into three groups: primary hypoadrenocorticism, or Addison's disease, whether it is due to tuberculosis, nonspecific destruction (atrophy) of the adrenal glands, or the Waterhouse–Friderichsen syndrome; secondary hypoadrenocorticism associated with hypopituitarism and Addison's disease in which the patient is already on adequate maintenance therapy with desoxycorticosterone and salt; surgical removal of adrenal tissue, as in treatment of Cushing's syndrome or the adrenogenital syndrome.

Primary Hypoadrenocorticism

Treatment of this condition is discussed step by step from the standpoint of the physician confronted with a case of Addisonian crisis.

Preliminaries. The patient is treated like a case of surgical shock — that is, put in the shock position, kept warm and disturbed as little as possible. A "coma" chart is started to record the following data: blood pressure, pulse, respirations, temperature by rectum and state of hydration (pulmonary congestion and peripheral edema). Intravenous and oral administration of fluids, treatment and urine volume are also charted. Data are being recorded every hour during the critical stages. Blood is drawn for the following determinations: sodium, chloride, potassium, nonprotein nitrogen, sugar, hematocrit and blood culture (about 25 cc. of blood suffices for these tests). Finally, cultures are made from the urine, throat and any obviously infected site to determine the precipitating cause of the crisis; the cerebrospinal fluid and sputum are cultured if indicated.

First stage. An intravenous injection of 1500 cc. of 5 per cent dextrose in isotonic saline solution is begun, followed by injection of 20 cc. of aqueous adrenocortical extract into the intravenous tubing (in severe cases, twice this amount is used), and 50,000 units of penicillin is then injected into the intravenous tubing.

All these measures should be under way within an hour of the time the diagnosis of acute adrenal insufficiency has been made.

Second stage. Aqueous extract, 10 cc. intramuscularly, is given every hour until the systolic blood pressure is 80 to 85 or above, then every two hours and finally every three hours if the blood

pressure is satisfactory. Lipo-Adrenal cortex, 1 cc. every four hours, is substituted after twelve to twenty-four hours if the systolic blood pressure is constant at 80 to 85 or above and then decreased gradually to 1 cc. every eight hours, continuing for three days after the patient is eating well. A slow intravenous drip of 5 per cent dextrose in isotonic saline solution is continued until the patient is able to tolerate frequent oral feedings; *the total amount of fluids given intravenously should not exceed 3000 cc. in the first twenty-four hours except in extreme dehydration.* Much less may be adequate in milder cases. It is possible to cause dangerous fluid retention (pulmonary edema) by too much fluid, since patients with hypoadrenocorticism have a characteristic difficulty in excreting "forced fluids."[3,4] Small oral feedings of fluids high in carbohydrate and protein every one or two hours are begun as soon as the patient can tolerate them well, usually during the second or third twelve hours of treatment. One hundred thousand units of penicillin is given intramuscularly every six hours for at least three days or until all signs of infection have been absent for several days; on the second day of treatment the culture results will be available, and a change in antibiotics can be made if necessary.

If the patient has been eating well for three days and has no signs of infection, all specific treatment can be stopped. Desoxycorticosterone medication can then be adjusted to maintenance levels, and the salt intake regulated.

On the above regimen, if all goes well, the patient should be much better in forty-eight hours. If, after the first four hours of treatment, the systolic blood pressure is not satisfactory (below 80) the following additional measures are recommended: if the temperature is elevated and the electrolyte pattern and hematocrit are normal, the dosage of adrenocortical extract is increased; if hemoconcentration persists an initial dose of 10 mg. of desoxycorticosterone is given intramuscularly, and 5 mg. every twelve hours unless edema develops. The dosage is reduced by half when the blood pressure reaches adequate levels. Plasma or concentrated human albumin should also be used in this situation.

It is only fair to add that one encounters cases of all degrees of severity. Experience and good judgment are necessary to decide how intensive and prolonged a program is indicated in a given case. The treatment described is for severe cases.

Secondary Hypoadrenocorticism

Treatment of this condition is designed for cases of panhypopituitarism and for cases of Addison's disease already on adequate maintenance doses of desoxycorticosterone. In these cases hypoglycemia tends to develop. The administration of too much fluid and sodium chloride must be carefully avoided.

The general plan of treatment* as indicated above under the discussion of primary hypoadrenocorticism is followed, except for the following changes: 10 per cent glucose in water instead of 5 per cent glucose in saline solution is given. Small, oral feedings high in carbohydrate and protein are started as soon as possible and before all the fluid has run into the veins and not more than 2000 cc. total fluids per twenty-four hours are used (a daily intake of 1000 cc. over the urine volume is sought). It is sometimes possible in milder episodes to avoid intravenous injection of fluids entirely, and this is desirable because of the danger of overhydration. Aqueous adrenocortical extract followed by Lipo-Adrenal cortex and penicillin are given as outlined above.

Patients in Whom Adrenal Tissue Has Been Removed

Therapy in cases of surgical removal of adrenal tissue for hyperadrenocorticism necessarily varies, depending upon the amount and nature of the adrenal tissue removed. So little experience with the management of this type of patient has accumulated that only a few general principles are mentioned here.

If substantial amounts of adrenal tissue are removed one should be prepared on short notice to institute an intensive therapeutic schedule, such as that outlined for primary hypoadrenocorticism. The management of patients with adrenal tumors associated with Cushing's syndrome constitutes a special and particularly difficult problem.[5-8] Since the tumor usually causes atrophy of the remaining adrenal tissue, the patient is plunged from hyperadrenocorticism into hypoadrenocorticism without opportunity for adjustments to take place. This situation often results in a prolonged, precarious postoperative course characterized by acute adrenal insufficiency in a severely depleted patient. These cases should be treated vigorously according to the schedule for primary hypoadrenocorticism outlined above. In addition, it is advisable, if possible, to use adrenocorticotrophic hormone (ACTH)† just before or immediately after operation to enlarge the remaining atrophied adrenal tissue. The use of potassium and amino acids parenterally may also be indicated.

Desoxycorticosterone has been omitted from the routine treatment schedules presented above. Its use in large doses is recommended almost universally in the literature.[11-14] However, all workers stress the complications that may arise with overdosage. The result is that we have used it with great cau-

*Recently, we have had occasion to treat 2 patients with panhypopituitarism in severe and prolonged crisis. Recovery in each case followed use of the above program, together with thyroxine and potassium intravenously. Both patients had normal or low serum potassium levels when their serum sodium and chloride were at very low levels (in sharp contrast to patients with Addison's disease, who have high serum potassium in crisis).

†It has been shown by a number of investigations[9,10] that highly purified preparations of adrenocorticotrophic hormone in doses of 75 to 100 mg. per day can stimulate all three major functions of the adrenal gland in twenty-four hours.

tion, probably in doses so small as to be relatively unimportant as compared with the other measures. The Mayo Clinic[15] has obtained good results without it. We recommend, therefore, that it be omitted as a routine measure. The doses suggested in the literature are: during the first twenty-four hours, 20 to 30 mg. intramuscularly divided into two doses at twelve-hour intervals, provided no edema occurs; thereafter, 5 to 15 mg. daily in two doses until the patient is eating well for several days, when the dosage is gradually adjusted to maintenance levels.

Prevention of Addisonian Crisis

Patients with adrenocortical hypofunction withstand stress poorly. It is therefore advisable to prepare them specially for any type of surgical procedure.

The following schedule is recommended for patients about to undergo major elective operations or childbirth, with the reservation that the procedure should be delayed for at least three weeks after recovery from a crisis, and until blood electrolytes and blood pressure are normal. The patient should receive a high-carbohydrate diet (at least 300 gm. daily), as well as 1 cc. of Lipo-Adrenal cortex every eight hours, for three days before operation. On the morning of operation, beginning several hours before the anesthetic is administered, the patient should be given 500 cc. of 5 per cent dextrose in isotonic saline solution to which 30 cc. of aqueous adrenal extract has been added. The intravenous infusion should be followed by whole-blood transfusion in amounts indicated by blood loss. Intravenous injections of 5 per cent dextrose in isotonic saline solution in amounts sufficient to maintain a daily urine output of 1000 to 1500 cc. should be continued until the patient is eating well. Finally, Lipo-Adrenal cortex should be continued, at doses gradually decreasing from 2 cc. every four hours to 1 cc. every eight hours, until the patient has been eating well for three days.

If Addisonian crisis develops despite these measures, treatment for primary hypoadrenocorticism outlined above should be started. If the patient must be subjected to an emergency surgical operation, the same schedule can be followed, 500 cc. of 5 per cent dextrose in isotonic saline solution containing 30 cc. of aqueous adrenal extract being given before operation.

For minor surgical procedures* such as multiple tooth extraction and biopsy, the following schedule is suggested: a light breakfast is allowed on the morning of the operation; frequent small feedings high in carbohydrate and protein are begun as soon as possible after the procedure; Lipo-Adrenal cortex, 1 cc. every eight hours, is given until the patient is eating well; when a tooth is to be extracted penicillin or sulfadiazine is administered one day before and two days after the procedure.

In all operations on patients with adrenocortical insufficiency, it is advisable to use local anesthetics whenever possible, and to avoid morphine and Avertin. If a general anesthetic is absolutely necessary, nitrous oxide, oxygen and ether, cyclopropane[11, 14] or nitrous oxide alone is the anesthetic of choice. It should be remembered that all sedatives and narcotics are to be used with the greatest caution in patients with adrenocortical insufficiency. If they are used, it should be in half the usual dosage. Codeine is said to be tolerated well by patients with Addison's disease.[11]

*Blood electrolytes and blood pressure should be normal before even minor elective procedures are undertaken.

Summary and Conclusions

Detailed programs for the management and prevention of acute adrenal insufficiency are presented. They are based on a review of the literature, and experience with 22 cases (1946-1949) in a large teaching hospital.

The suggested schedules are necessarily tentative and arbitrary, simply because too little data and experience have accumulated to permit dogmatism. It is hoped that they will be given a careful trial to make constructive criticism possible and thereby to improve the treatment of the disease.

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PARA-AMINOSALICYLIC ACID (PAS) IN CHRONIC PULMONARY TUBERCULOSIS*

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IT HAS been shown that para-aminosalicylic acid (PAS) has a definite bacteriostatic effect on human strains of *Mycobacterium tuberculosis* in vitro[1-4] and in vivo.[3-9] It is also known that its tuberculostatic potency is considerably less than that of streptomycin.[5, 6] However, the emergence of streptomycin-resistant tubercle bacilli after treatment with streptomycin constitutes an important restriction on its use in the therapy of pulmonary tuberculosis and necessitates careful timing and co-ordination of streptomycin treatment with the total therapeutic attack. Since retreatment with streptomycin for exacerbations and reactivations is often futile, it is frequently necessary to withhold this drug for use at the optimal time. For these reasons it is desirable that the effect of other antimicrobial agents be established in various types of tuberculosis. The purpose of this report is to present data on a series of patients with chronic pulmonary tuberculosis treated with PAS.

METHOD OF STUDY

A total of 22 patients, 8 males and 14 females, were selected for study. The patients varied in age from eighteen to seventy years. All but 1 had advanced bilateral pulmonary tuberculosis with sputum positive for tubercle bacilli. The exception was a patient with tuberculous pericardial effusion from which tubercle bacilli highly resistant to streptomycin had been cultured. All patients had lesions of long standing, and prolonged bed rest had not produced definitive improvement or sputum conversion in any of the series.

Twenty-three courses of PAS|| were given, ranging from thirty to three hundred and twelve days, with a median duration of treatment of one hundred and twenty-one days. The dosage was 10 to 15 gm. daily. Half the patients received capsules containing 0.5 gm. of PAS, and the remainder a liquid formula made up as follows: PAS, 100 gm.; sodium bicarbonate, 60 gm.; oil of wintergreen, 5 drops; and distilled water to make 500 cc. The total daily dose was given in divided portions every four hours, with omission of one dose at night.

At the beginning of the study, base-line laboratory tests were performed on all patients. These included complete blood counts, urinalyses, erythrocyte sedimentation rates (Westergren method), chest roentgenograms and examinations of sputum for tubercle bacilli by smear, concentration and culture. These tests were repeated weekly or biweekly throughout the period of the study. Bronchoscopic examination was performed in 14 of the 22 patients prior to therapy, those showing endobronchial lesions being re-examined during and after treatment. Serial hepatic-function tests were performed in 5 cases, with electrocardiograms and tomograms when indicated.

OBSERVATIONS

During the period of treatment 14 of the 22 patients showed symptomatic improvement, consisting of reduction in cough and sputum, decrease in wheezing and fever, increase in appetite, gain in body weight and augmented sense of well-being. Seven were not improved symptomatically, and 1 felt worse. Serial roentgenograms of the chest showed improvement in 12 of the group; in 8 there was no radiographic change, and in 2 there was radiographic evidence of progression of the lesions. Of the 14 patients in whom bronchoscopic examination was performed before treatment, 4 showed endobronchial tuberculosis. Three of these 4 showed improvement in the endoscopic appearance of the lesions after treatment, and 1 was worse.

In 5 patients the parenchymal lesions were stabilized with PAS preparatory to performance of additional therapeutic procedures — that is, artificial pneumothorax in 2, thoracoplasty in 1 and pneumonectomy in 2. Nine patients whose lesions had been progressive on bed rest improved and attained a quiescent status. Two patients (Cases 13 and 14) improved during treatment, but showed evidence of prompt retrogression after cessation of PAS therapy (Table 1). Cavity closure was obtained in only 1 case treated with PAS alone (Case 6), and actual progression of lesions during therapy was observed in 2 (Cases 5 and 11).

Except in the case of tuberculous pericarditis (Case 16) the sputum of all patients prior to PAS therapy contained tubercle bacilli demonstrable on direct smear. At the termination of treatment, 13 patients still had positive smears, although fewer organisms were seen in some cases. Eight patients showed significant improvement in bacteriologic status. Of these, 5 had negative smears and concentrates, cultures of sputum or gastric contents remaining positive (Cases 8, 13, 14, 15 and 17), and 3 had negative cultures as well as smears and concentrates (Cases 1, 6, and 22). The latter 3 remain consistently negative for tubercle bacilli

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||The PAS used in this study was kindly supplied by Merck and Company, Incorporated, Rahway, New Jersey.

TABLE 1. *Results of Treatment with PAS in Chronic Advanced Pulmonary Tuberculosis.*

Case No.	Age	Sex	Character of Lesion	Daily Dose	Duration of Treatment	Effects During Treatment				Period Since Termination of Therapy	Present Status
						Symptoms	X-ray	Bronchial Lesion	Sputum		
	yr.			*gm.*	*days*					*mo.*	
1	20	F	Fibroexudative, bilateral, moderately advanced, slowly progressive; tuberculous bronchitis.	10	150	Improved	Improved	Improved	Negative on culture	13	Patient discharged apparently arrested; cultures negative.
2	70	M	Caseocavernous, bilateral, far advanced, progressive	10–15	121	Improved	Improved	None	Positive on smear	8	Disease quiescent
3	37	F	Fibrocaseocavernous, far advanced, stationary (bilateral pneumothorax)	15	85	Unimproved	Unimproved	None	Positive on smear	9	Disease quiescent
4	25	M	Caseocavernous, bilateral, far advanced, progressive	15	221	Improved	Improved	Worse	Positive on smear	4	Patient improved; pneumonectomy on right successfully performed.
5	27	F	Caseocavernous, bilateral, far advanced, progressive	15	51	Worse	Worse	—	Positive on smear	—	Patient dead
6	29	F	Fibrocavernous, bilateral, moderately advanced, slowly progressive	15	179	Improved	Improved	None	Negative on culture	6	Disease apparently arrested; cavity remains closed; cultures negative.
7	32	F	Fibrocavernous, bilateral, far advanced, stationary; post-thoracoplasty (left).	10–15	82	Unimproved	Unimproved	None	Positive on smear	11	Patient unimproved
8	29	F	Fibrocaseous, bilateral, far advanced, slowly progressive; post-thoracoplasty (left).	10–15	101	Improved	Improved	None	Negative on smear and concentrate; positive on culture.	11	Patient well and working; occasional positive culture.
9	43	M	Fibrocaseocavernous, bilateral, far advanced, progressive; tension cavity in right upper lobe.	15	99* 30	Unimproved	Unimproved	—	Positive on smear	8	Patient unimproved; tension cavity shows spontaneous changes.
10	19	M	Caseocavernous, bilateral, far advanced, progressive	10–15	140	Improved	Improved	None	Positive on smear	9	Patient improved; receiving right artificial pneumothorax.
11	38	M	Fibrocaseous, bilateral, far advanced, progressive	10–15	49	Unimproved	Worse	—	Positive on smear	—	Patient dead
12	59	M	Fibrocaseocavernous, bilateral, far advanced, progressive	10	54	Unimproved	Improved	None	Positive on smear	14	Disease quiescent
13	28	F	Fibrocaseocavernous, bilateral, far advanced, progressive on left (artificial pneumothorax on right)	10–15	191	Improved	Markedly improved	None	Negative on smear and concentrate; positive on culture.	5	Cavity in left upper lobe reopened; patient receiving artificial pneumothorax (left).
14	38	F	Fibrocaseocavernous, bilateral, far advanced, progressive	15	312	Improved	Improved	Improved	Negative on smear and concentrate; positive on culture.	1	Cough, sputum and fever increased; PAS treatment reinstituted.
15	21	F	Fibrocaseocavernous, bilateral, far advanced; cavities in both upper lobes retrogressive, following cavernostomy on left.	10–15	145	Improved	Improved	None	Negative on smear and concentrate; positive on culture.	11	Cavity in right upper lobe closed; thoracoplasty (left) successfully performed.
16	18	F	Tuberculous pericarditis, postpneumonectomy (left).	5–12.5	32	Unimproved	Unimproved	—	Unimproved; pericardial exudate positive on culture.	—	Patient dead
17	20	F	Caseocavernous, bilateral, far advanced, progressive	5–12.5	169	Improved	Unimproved	Improved	Negative on smear and concentrate; positive on culture.	—	Patient dead (postpneumonectomy spread)
18	34	F	Fibrocaseocavernous, bilateral, far advanced, progressive; tuberculous empyema.	15	216	Improved	Improved	—	Positive on smear	1	Disease quiescent; empyema improved.
19	58	M	Fibrocaseocavernous, bilateral, far advanced, progressive	10–15	104	Improved	Improved	None	Positive on smear	5	Disease quiescent
20	46	F	Fibrocavernous, bilateral, far advanced, stationary	15	30	Unimproved	Unimproved	—	Positive on smear	11	Patient unimproved
21	63	M	Fibrocaseocavernous, bilateral, far advanced, progressive	10	129	Improved	Unimproved	—	Positive on smear	13	Disease quiescent
22	35	F	Fibrocaseous, bilateral, far advanced; slowly progressive, tuberculous bronchitis.	10	130	Improved	Unimproved	Improved	Negative on culture	13	Patient discharged with disease arrested; cultures negative.

*Two courses of treatment.

on cultures of sputum and gastric contents to date, five, thirteen and thirteen months respectively after termination of PAS therapy. As with streptomycin, there were cases in which the smear during PAS treatment was positive and culture of the same specimen negative. Such specimens were considered positive.

Toxic Reactions

Only 3 of the 22 patients in the group did not have gastrointestinal symptoms at some time during treatment. In these 3 PAS was taken regularly for fifty-one, one hundred and forty-five and two hundred and sixteen days respectively, without discomfort of any kind. The others all complained of varying degrees of epigastric distress, which usually disappeared or diminished after the first two or three weeks on PAS or after interruption of treatment for twenty-four to forty-eight hours. Slight nausea, vomiting and diarrhea occurred frequently. In only 1 case, however, was it necessary to stop treatment because of severe gastrointestinal effects. Several patients who tolerated 10 gm. of PAS daily without discomfort could not take larger doses. No consistent correlation was found between the form in which the drug was ingested (liquid formula or capsule) and the severity of the gastrointestinal symptoms.

In 1 patient (Case 13) mild hepatitis developed during the third week on PAS. In the next three weeks, during which she was not given the drug, the signs and symptoms of hepatitis subsided, and liver-function tests returned to normal. She was then given PAS again for five months, without evidence of exacerbation, and the liver-function tests remain normal to the present time, ten months after the original episode. Repeated determinations of cephalin-cholesterol flocculation, thymol-turbidity, bromsulfalein excretion, and serum bilirubin were performed on 4 other patients receiving PAS. There was no evidence of hepatic damage in any of these patients. It is probable that the case cited was one of coincidental infectious hepatitis.

A febrile reaction was observed in 1 patient in the group (Case 16). A temperature of 105°F. developed after five weeks of PAS administration, and a 2-gm. provocative dose of PAS given twelve days after cessation of therapy was followed within two hours by reappearance of fever (maximum temperature of 105°F.) and severe tachypnea. A sensitivity to the drug was apparent, but no immunologic or skin tests were done.

The presence of reducing substances in the urine was repeatedly demonstrated in patients receiving PAS. These substances were identified as probably glucuronates. Weekly urinalyses and blood counts showed no other abnormality. Hypoprothrombinemia was demonstrated in 1 patient (Case 9). This was corrected with transfusions of whole blood and administration of vitamin K parenterally. Determinations of the prothrombin time on the same patient were normal during a second course of PAS therapy, as were the prothrombin times in 6 other patients receiving PAS.

Discussion

The unfavorable character of the lesions in the cases treated is apparent. Five of the patients had been unaffected by previous streptomycin therapy, and 9 others had relapsed after it. Collapse therapy or pulmonary resection had failed in several cases, and with the exception of 1 patient, who refused thoracoplasty, the cases were unsuitable for any other form of treatment. The severity of the process in these patients is further emphasized by the fact that 4 of them have already died of progressive tuberculosis. The attainment of symptomatic improvement in over two thirds and roentgenographic improvement in more than half of the patients in such a group is of some significance.

Of equal interest was the effect observed on the sputum of patients receiving PAS. In 3 the sputum and gastric contents became negative for tubercle bacilli on cultures and remained so. In 5 additional cases with highly positive direct smears before treatment, smears of the concentrates became negative for tubercle bacilli. Dosage of the infecting organism is probably an important factor in dissemination of tuberculosis to contacts. The suppressive action of PAS on the quantity of the sputum and its content of tubercle bacilli in patients with open lesions may have a place in the management of such cases from the public-health viewpoint. More data concerning the emergence of organisms resistant to PAS after treatment are needed before use of the drug for this purpose can be recommended. There is evidence that PAS-resistant organisms occur,[7, 10, 11] but it is possible that their emergence can be delayed or prevented by combination of administration of PAS with streptomycin or Promin.[10, 12]

It should be emphasized that the sputum in more than half the patients continued to be positive for tubercle bacilli on direct smear during and after treatment. Cavities usually do not close with PAS therapy alone, and its use should not be permitted to postpone institution of collapse therapy that is indicated and feasible. The drug is occasionally helpful in bringing a previously unsuitable patient to the point where collapse measures or excisional surgery may be employed, but it is no substitute for these procedures.

The frequency of gastrointestinal effects did not prevent administration of the drug over long periods. The febrile reaction observed was probably similar to the sensitivity occasionally seen with other salicylates. Kierland and Carr[13] have recently reported 2 cases of reactions to PAS with fever and cutaneous eruptions. Intradermal skin tests

and patch tests were performed in these cases and were negative. In 1 case the eruption was reproduced by administration of sodium salicylate but not by para-aminobenzoic acid, indicating that the patient was probably sensitive to the salicylic acid radical of the PAS.

The 1 case of hypoprothrombinemia observed in the present series was not confirmed in any other patient or in the same patient on repeated administration of the drug. It is known that large doses of other salicylates may depress prothrombin levels, but since hepatic dysfunction has also been demonstrated in a large number of patients with far advanced tuberculosis who were not receiving PAS,[14] this effect cannot be attributed to the drug. In this connection it may be noted that the intravenous use of the sodium salt of PAS, without evidence of liver damage, has recently been reported.[15]

Since this report was presented for publication, valuable reviews on the subject[16, 17] have appeared in the American medical literature. The articles themselves should be consulted for details.

Summary and Conclusions

Twenty-two patients with advanced chronic pulmonary tuberculosis were given twenty-three courses of PAS in dosage of 10 to 15 gm. daily for periods of thirty to three hundred and twelve days.

The toxic reactions to the drug were minimal and consisted chiefly of gastric irritation, nausea, vomiting and diarrhea. One febrile reaction was observed. There was no definite evidence of hepatic or renal damage, and the peripheral blood picture was not altered.

Fourteen of the 22 patients manifested symptomatic improvement during the therapy.

Twelve of the 22 patients showed roentgenographic improvement, 8 showed no roentgenographic change, and in 2 there was roentgenographic evidence of progression of the pulmonary lesions during therapy.

Of 4 patients who had active tuberculous bronchitis prior to therapy, 3 showed improvement in their endobronchial lesions.

Three of the 22 cases became negative for tubercle bacilli on examinations of the sputum and gastric contents by culture, 5 became negative on smears of sputum concentrates, and 13 remained positive on direct smears of the sputum.

It appears that PAS is a drug of relatively low toxicity in man and that its use is indicated in the following types of pulmonary tuberculosis: progressive chronic caseous or fibrocaseous lesions in cases not immediately suitable for collapse therapy or pulmonary resection; active endobronchial tuberculosis with a streptomycin-resistant organism, or prior to streptomycin therapy when it is advisable to withhold streptomycin for probable need at a later date; and experimentally, in combination with other antimycobacterial agents and in early and exudative noncavitary lesions that do not respond promptly to bed rest.

Progression of pulmonary lesions may occur during PAS treatment. When collapse therapy or pulmonary resection is indicated, the availability of antibacterial substances should not be permitted to delay more definitive therapy.

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PANCYTOPENIA DUE TO MESANTOIN*

Report of a Case

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SINCE the introduction of Mesantoin (3 methyl-5, 5-phenylethyl-hydantoin) as an anticonvulsant a number of cases of depression of bone marrow, thought to be due to this drug, have been reported.[1-5] We wish to add another case of pancytopenia due to Mesantoin.

CASE REPORT

B. L. Z., a 28-year-old pharmacy student, was admitted to the hospital on August 3, 1948, complaining of multiple bruises, spontaneous nosebleeds, sore throat, chills and fever. In August, 1947, while in bed, he experienced an episode characterized by tonic and clonic movements of the body, arms and legs and subsequent mental confusion. This was diagnosed as grand-mal epilepsy. An electroencephalogram was done and was said to be normal. The patient was placed on diphenylhydantoin sodium, 0.1 gm. three times daily. This medication was discontinued in November. In December the patient had another seizure, and diphenylhydantoin was again prescribed; however, shortly thereafter the drug had to be discontinued because of soreness of gums. Mesantoin, in doses of 0.3 gm. daily, was then substituted. In February, 1948, he had an erythematous rash of the extremities followed by desquamation of the skin of the hands. Anticonvulsant medication was continued. Three weeks prior to admission the patient had spontaneous epistaxis and noted an ecchymotic area on the left thigh. Mesantoin was discontinued, but transient epistaxes continued and many petechiae and ecchymoses developed. Two weeks prior to admission the white-cell count was 1850. Purpuric areas continued to develop and the patient had a severe occipital and parietal headache not relieved by ordinary medications. Two days prior to admission, a severe sore throat, which was associated with chills and fever, developed. At this time he also noted that his stools were tarry.

Physical examination revealed a well developed and well nourished man, who exhibited moderate pallor of the skin. The mucous membranes of the eyes, nose and mouth were pale, and one petechia of the left tarsal conjunctiva was noted. No retinal hemorrhages were observed on ophthalmoscopic examination. A 4-mm. purpuric lesion was seen on the tip of the tongue. The right tonsillar fossa was reddened, inflamed and covered with exudate. The lymph nodes were not enlarged, and the lung fields were clear. The heart was normal. The liver and spleen were not palpable. Neurologic examination was noncontributory. Multiple ecchymoses were observed over the right forearm and both thighs, and many petechiae were seen over both arms and over the posterior surfaces of the thighs.

The temperature was 99.8°F., the pulse 78, and the respirations 18. The blood pressure was 110/86.

Examination of the blood disclosed a red-cell count of 2,550,000, with a hemoglobin of 8.2 gm. per 100 cc., and a white-

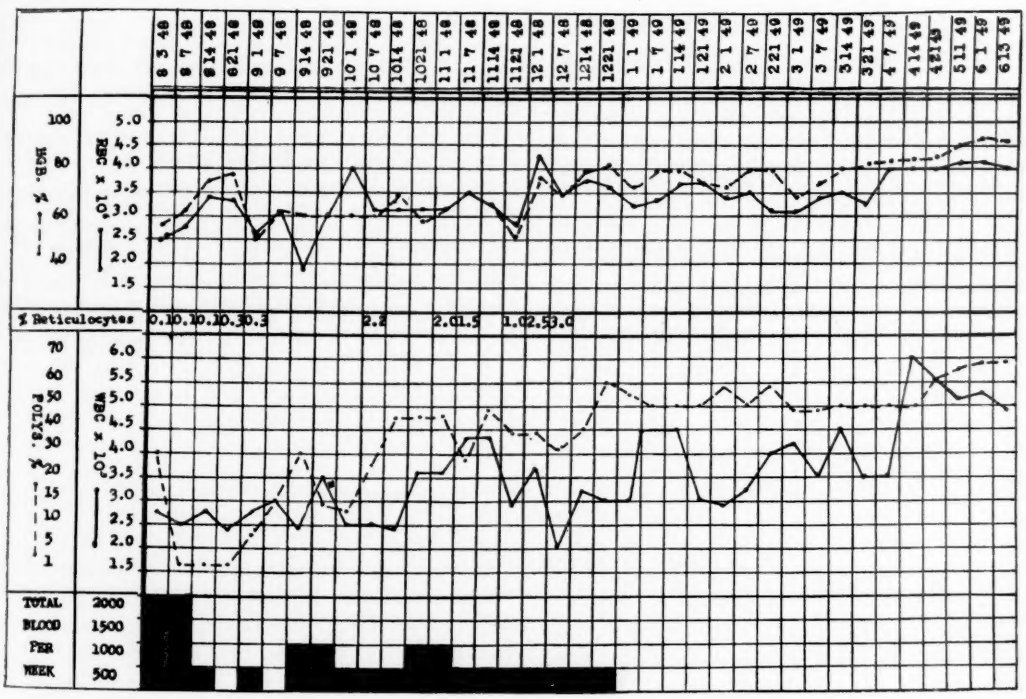

FIGURE 1. *Response to Blood Transfusions and Other Therapy.*

*Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and the conclusions drawn by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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cell count of 2700, with 34 per cent neutrophils, 65 per cent lymphocytes and 1 per cent eosinophils. The platelet count was 65,000 (subsequent platelet counts varied from 110,000 to 300,000). The bleeding time was 1½ minutes, and the coagulation time 2 minutes (Lee and White method). Morphology of the stained blood cells was normal. The blood was Type A, Rh +. The standard Kahn serologic test was negative. The prothrombin time was 10 seconds. Examination of the stool revealed a faintly positive guaiac test. A culture from the tonsillar fossa showed hemolytic *Staphylococcus aureus* and nonhemolytic streptococci. The serum bilirubin was 0.6 mg. per 100 cc. on August 6. Routine urinalysis was negative on admission.

Sternal punctures were done on August 6 and 18. There was a conspicuous absence of cellular elements usually present in bone marrow. The nucleated cells were almost exclusively lymphocytes.

X-ray examination of the chest demonstrated no abnormalities. Two splenograms disclosed no enlargement of the spleen.

Frequent transfusions of whole blood were begun, and 50,000 units of penicillin was given intramuscularly every 3 hours. The temperature varied from 98.2 to 102°F. daily during the first 3 hospital days, and the penicillin dosage was increased to 100,000 units every 3 hours and continued during the next 28 hospital days, when there was an afternoon temperature of 99.2 to 100°F. On the 31st hospital day the patient became afebrile. Gross hematuria was noted on August 12, persisting intermittently until September 4. From that time repeated urinalyses were negative. Tarry stools were observed from August 29 to September 3. New purpuric areas continued to appear until September 5. From that date the patient was asymptomatic. Occasional blood transfusions were needed to maintain an adequate level of hemoglobin. The bone marrow gradually resumed its function, as manifested by an increasing proportion of polymorphonuclear elements and a rise in reticulocyte response (Fig. 1). In addition to transfusions of whole blood the patient was treated at various intervals with rutin, ascorbic acid, ferrous sulfate, crude liver extract (intramuscularly) and yellow extract of bone marrow.

He was discharged from the hospital on January 4, 1949. During subsequent follow-up studies he was found to be in good health, and the blood picture remained within normal limits.

Discussion

Of the 6 previously reported cases of depression of bone marrow due to Mesantoin, 4 terminated fatally. In 2 of the 4 a skin rash preceded the hematologic disorder. In the case reported above, the patient gave a history of erythematous skin rash with desquamation occurring about six months prior to admission to the hospital. The incidence of skin rash during Mesantoin therapy varies from 10 to 14 per cent; it should be considered a sign of sensitivity to the drug and the patient should be observed very carefully for more serious toxic disturbances. It would be wise, as suggested by Ruskin,[1] to follow all patients on Mesantoin medication with occasional blood counts. From a review of the literature, one must conclude that Mesantoin is by no means an innocuous drug.

Summary

A case of pancytopenia due to Mesantoin, preceded by a skin rash and with ultimate recovery, is reported.

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MEDICAL PROGRESS

THE CLINICAL USEFULNESS OF ACTH AND CORTISONE (Concluded)*

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DISEASES IN WHICH ACTH AND CORTISONE MAY BE USEFUL (Continued)

Regional Enteritis

Astwood,[25] using his preparation of ACTH, administered for nine to twenty days in doses of 20 mg. every six to eight hours, observed improvement in 4 patients with regional enteritis. The improvement was characterized by an increased appetite, weight gain, relief of abdominal pain, decreased frequency of bowel movements and improved sense of well-being. One of the 4 patients has relapsed.

Pulmonary Beryllosis

Browne[131] reported the use of ACTH in a patient with pulmonary beryllosis who obtained partial improvement. Our experience has been limited to a thirty-two-year-old woman with marked clinical and x-ray evidence of pulmonary beryllosis. ACTH (20 mg. every six hours) was administered for eight days. The clinical and subjective improvement was unequivocal after four days of treatment. The patient became less orthopneic and had much less dyspnea on mild exertion. After eight days of therapy an x-ray film of the chest showed definite diminution in the diffuse mottled density noted in the initial film.

DISEASES IN WHICH ACTH AND CORTISONE ARE OF QUESTIONABLE VALUE

ACTH and Cortisone have not been consistently beneficial in the diseases placed in this category, although results have been sufficiently encouraging to make the use of these agents desirable under special conditions. Thus, the results in mental disease are far from uniform; myasthenia gravis, although made worse during therapy, is subsequently improved; in tuberculosis, allergic manifestations are abolished, and yet there are serious theoretical limitations to the use of these agents in this disease. Other diseases cited present similar problems in management.

Mental Disease

Interest in the therapeutic use of ACTH and Cortisone in patients with mental disease has been stimulated by the observations of Pincus and his collaborators,[132] who demonstrated that the adrenocortical response to stress or ACTH is subnormal in schizophrenia. Therapeutic trials in such patients have thus far been inconclusive.[133]

Preliminary studies of the effect of ACTH on patients with severe manifestations of alcoholism appear more promising.[134] In both acute alcoholic intoxication and delirium tremens it is reported that the drug markedly speeds recovery, as compared to that anticipated from conventional therapy. No favorable effect has been observed in Korsakoff's psychosis.

We have used ACTH in an attempt to alleviate withdrawal symptoms in patients with narcotic addiction. In 1 patient in whom exacerbation of asthma had defeated previous attempts to withdraw Pantopon, the administration of ACTH controlled the asthma during successful withdrawal. In 2 patients with severe personality disorders, 1 addicted to codeine and the other to morphine, attempts at withdrawal during ACTH therapy were unsuccessful.

Multiple Sclerosis

Randt, Traeger and Merritt[135] have studied the effect of ACTH in 2 female patients with multiple sclerosis. In 1, the disease was of short duration (seven months), and ACTH administration, 1300 mg. over an eight-day period, led to an improvement in the neurologic status, as evidenced by lessened dysarthria, reduced spasticity and a reduction in hyperactivity of the deep tendon reflexes. These neurologic changes lasted only two weeks after ACTH. In the second patient, who had multiple sclerosis of seven years' duration, ACTH treatment, 1600 mg. over a nine-day period, had no remarkable effects. Of interest in both cases was the reduction in the cerebrospinal-fluid total protein and gamma globulin.

Pemphigus

In 1940, Talbott, Lever and Consolazio[1, 136] reported on the partially successful treatment of pemphigus with adrenocortical extract in doses of

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10 to 20 cc. daily in patients showing electrolyte changes similar to those seen in adrenocortical insufficiency.

We have studied an adult male with a malignant form of pemphigus vulgaris of two years' duration, whose disease was progressing, despite antibiotic therapy, large doses of vitamin D and calcium. This patient was treated with 100 to 200 mg. of ACTH daily for a period of twenty days; 100 to 200 mg. of Cortisone was also given from the fourteenth through the seventeenth day. An adequate adrenocortical response to ACTH was indicated by the rise in urinary 17-ketosteroid excretion from a value of 5 mg. to a level of 19 mg. per day. The progress of the skin lesions was arrested, and considerable healing of the denuded areas occurred. The patient died during therapy from an overwhelming *Staphylococcus aureus* septicemia, which proved resistant to all chemotherapeutic and antibiotic agents.

Adrenocortical hormones appear to be of benefit in pemphigus. It is of interest not only that the progression of the skin lesions was halted but also that epithelialization was stimulated.

Scleroderma

Bayles and his associates[137] have recently reported their experience with 4 cases of scleroderma given ACTH in doses of 5 to 10 mg. every six hours for two or three weeks. During treatment there was moderate clinical improvement: appetite improved; joint pains, when present, disappeared, and there was some diminution of joint stiffness, tightness of the skin and dysphagia; 1 patient with epigastric pain enjoyed some relief from this symptom. None of these effects were maintained after the drug was stopped, and all patients returned to their former status two or three weeks later. Skin biopsies showed no change in the pathological histology. Our own limited experience has been quite comparable. One patient whose principal complaints were tightness of the skin and epigastric pain experienced no relief from two weeks' treatment with ACTH in doses of 25 to 40 mg. every six hours; a second patient, suffering predominantly from polyarthralgia and joint stiffness, received only moderate relief from Cortisone in doses of 25 to 50 mg. every six hours for three weeks. In summary, then, it appears that, although both ACTH and Cortisone are capable of inducing transient amelioration of the signs and symptoms of the scleroderma, there is as yet no evidence that they in any way alter the fundamental course of the disease.

Myasthenia Gravis

The first available clinical report of the use of ACTH in myasthenia gravis is that of Soffer et al.,[138] who observed striking improvement in a female patient with a thymic tumor treated for four days (50 mg. daily). This improvement, accompanied by a reduction in the size of the thymoma, lasted for two months, but the tumor began to enlarge three weeks after ACTH was stopped. Since then Hellman[139] and Torda[140] have reported several cases of myasthenia gravis treated with ACTH. Generally speaking, the experience of these workers and others[141] has been that ACTH produces an adverse effect, an intensification of symptoms during its administration, improvement being noted only *after* ACTH has been discontinued. This has consisted chiefly of a reduction in Prostigmine requirement. In critically ill patients the intensifying of symptoms during ACTH has proved almost fatal.[142] Hellman[139] has given Compound A to 2 patients with myasthenia gravis and observed striking temporary improvement. Sprague[143] reported no improvement in a patient treated with Cortisone.

The value of ACTH in myasthenia gravis at present is questionable. It cannot be recommended for general use since it may be associated with a severe, possibly fatal, exacerbation of symptoms. Soffer[144] suggests that the drug may be employed as a means of ascertaining which patients with thymic tumors are likely to respond favorably to surgical removal since fibrous thymic tumors, which are unresponsive to ACTH, are not likely to be followed by any symptomatic response when removed surgically.

Osteoarthritis

One patient with a generalized osteoarthritis and an associated bilateral malum coxae senilis was treated with ACTH (10 mg. every six hours) for seven days. Placebos given during the preceding two days had no effect. There was a marked alleviation of pain and increased mobility of joints within twenty-four hours of the start of ACTH. Improvement became more marked during the seven-day course of therapy. The response in this patient serves as a caution against attempting to diagnose the type of joint disease on the basis of a subjective response to ACTH or Cortisone.

Paget's Disease

Albright and Bartter[145] used ACTH in a forty-five-year-old man with severe Paget's disease. The daily dose employed was 34 mg. for six days and 43 mg. for twelve days in four divided doses. The alkaline serum phosphatase declined progressively from 60 to 3 Bodansky units six days after therapy had been discontinued. No increase in the urinary excretion of calcium was observed, nor did a significant change in the clinical condition of this patient occur.

Tuberculosis

One patient with far advanced pulmonary tuberculosis was given 100 mg. of ACTH per day for twelve days.[146] During treatment, the temperature and pulse became normal; the sputum and thoracotomy drainage diminished, drenching night sweats

ceased, appetite became ravenous, and a marked sense of well-being developed. The sedimentation rate fell to normal; the in vitro tuberculin cytolysis test fell to zero, and the tuberculin skin test became negative. A chest film showed no significant change. After discontinuance of ACTH, there was an exacerbation of the disease.

ACTH induced similar clinical changes in 2 other patients with tuberculosis.[147] In 1, there was definite spread of the tuberculosis during the period of administration.

Through inhibition of tissue hypersensitivity, adrenal steroids may *either* ameliorate the severity *or* facilitate the spread of established tuberculous infection. Since it is not yet safe to predict which action will predominate in a given case of tuberculosis, further investigation must be undertaken. The possibility remains that these compounds will prove of value when given in conjunction with specific antibiotic agents.

Pneumonia

Finland and his co-workers[148] have reported dramatic defervescence and clinical improvement in a case of classic lobar pneumonia on the third day of the disease, after the institution of ACTH therapy, and this observation has been repeated in several subsequent cases. It is encouraging to suppose that the adrenal steroids promote defervescence by interfering with tissue reactions to the invading organisms in a manner analogous to their inhibition of allergic reactions. Such a mechanism is compatible with the isolation of Type 8 pneumococci from the blood of the published case of Finland et al.[148] at a time when the temperature was normal and the patient was feeling remarkably improved.

The same workers report a favorable response to ACTH in cases of primary atypical pneumonia. Fever resistant to antibiotics was abolished, and symptoms greatly ameliorated; relapse was observed when the drug was discontinued.

Anoxia

An increased tolerance for low oxygen tension has been demonstrated in animals treated with adrenal extracts, or with ACTH.[149] In man[150] ACTH, 100 mg. daily given in four divided doses over a forty-eight-hour period, has no appreciable effect on tolerance to acute anoxia. However, 160 mg. daily, administered in divided doses over a period of two to five days produces an increase in simulated altitude tolerance of 2000 to 3000 feet above previous basal levels.

Pernicious Anemia

ACTH was administered by Gardner[60] to a fifty-two-year-old woman with pernicious anemia who had had liver therapy up to one month prior to treatment with ACTH. The reticulocyte count was 1.1 per cent, and the hematocrit 22 per cent. The patient was given 15 mg. of ACTH every six hours (total daily dose 60 mg.) for an eight-day period. On the eighth day of therapy the reticulocytes had increased to 6.3 per cent and by the following day were 7.5 per cent. They remained at that level for five days, after which they fell to the initial level. The reticulocytosis was accompanied by a rise in nucleated red cells, which attained a maximum of 52 per cent of the total count two days after termination of ACTH therapy. There was no significant rise in the red-cell count, presumably because of the short duration of treatment. Bone-marrow aspiration revealed a marked change in the red-cell series from a very immature to a mature type of cell. This picture reverted to pretreatment status nine days after cessation

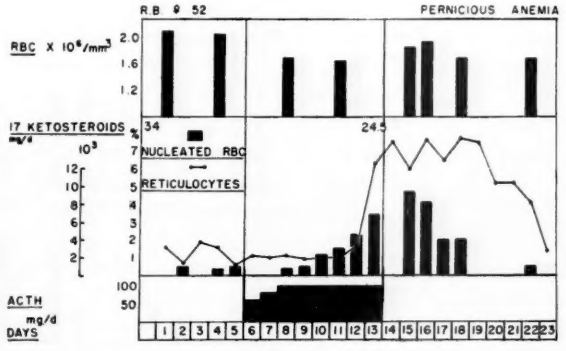

FIGURE 8. *Effect of ACTH on Pernicious Anemia, Showing Reticulocytosis Beginning on the Seventh Day of Therapy.*

of ACTH. The customary polymorphonuclear leukocytosis was observed after adrenocortical activation, and the 17-ketosteroids rose from an initial value of 3.4 mg. per day to 24.5 mg. in the course of treatment (Fig. 8).

In contrast, a young woman with *aplastic anemia* treated with ACTH for eighteen days with a total dosage of 1060 mg. failed to show any hematologic change whatsoever. There was no evidence of bone-marrow regeneration, although adequate adrenocortical activation was indicated by a marked rise in 17-ketosteroid excretion during treatment.

These studies suggest that ACTH favors the release of preformed elements from the bone marrow and may increase the rate of maturation, but is not capable of inducing bone-marrow regeneration.

Liver Disease

Studies of the effects of ACTH on both the chronic and acute forms of liver disease have been carried out. Bluemle and his co-workers[151] met with encouraging results in 1 of 2 cases of alcoholic cirrhosis and in a case of chronic viral hepatitis treated with ACTH. In the patient with alcoholic cirrhosis in whom beneficial effects were noted a severe por-

tal fibrosis was observed by biopsy before treatment. Another biopsy taken after a seven-day course of ACTH (500 mg.) showed a "decrease in the amount of fibrosis and regeneration of normal appearing liver tissue." The same investigators treated 2 cases of acute viral hepatitis with ACTH, without evidence of improvement.

Our experience has been limited to 2 cases of liver disease. In 1 patient homologous serum jaundice was superimposed upon an aplastic anemia. The patient was gravely ill, and ACTH was administered over an eighteen-day period in a total dosage of 1060 mg. An immediate clinical improvement, rapid loss of fever and marked increase in appetite was accompanied by improvement in liver-function tests (Fig. 9). In a patient with jaundice and liver disease due to methyltestosterone therapy of the type described by Werner and his associates[152] a marked increase in appetite and improved sense of well-being were not followed by an immediate, sustained improvement in liver function.

The role of ACTH in the alteration of liver disease is open to considerable speculation. One is impressed by the early, rapidly developing *improvement in appetite* and *sense of well-being* observed. In the treatment of liver disease the advantages of a high-calorie, highly nutritious diet are well established. It is known that 11,17-oxysteroids increase hepatic glycogen reserves and in patients with Addison's disease improve the capacity of the liver to enhance conjugation and detoxification.[153] ACTH will probably find a useful place in the treatment of liver disease, particularly when severe anorexia and poor nutrition are contributory factors.

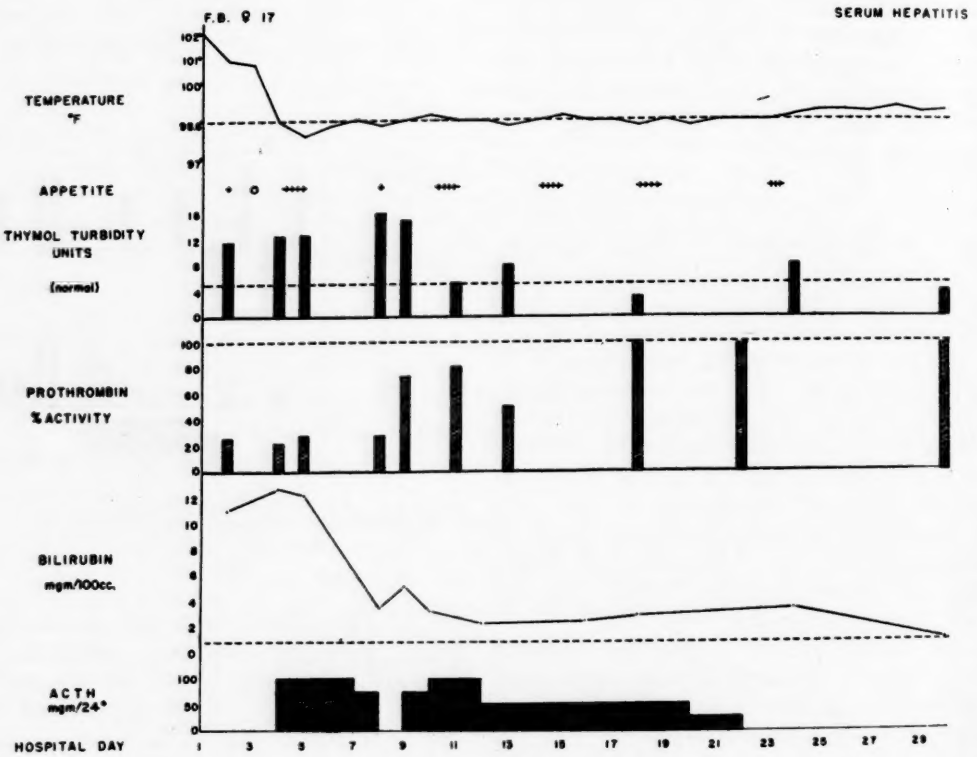

FIGURE 9. *Effect of ACTH on Acute Hepatitis.*

Thyrotoxicosis

We have studied the effect of ACTH in 6 patients with Graves's disease. The dosage employed was 40 to 200 mg. per day for periods of five to twenty-three days.[28, 29] In all patients an initial exacerbation of thyrotoxicosis occurred during the first twenty-four hours of therapy. In 3 patients no improvement was observed. In the other 3 decrease in gland size and a decrease in the I-131 accumulation gradient and in the serum protein-bound iodine was associated with clinical improvement. Two of these 3 patients had a significant fall in basal metabolic rate during the period of therapy. In 1 patient improvement was sufficient to permit subtotal thyroidectomy without other preoperative medication. In another there was a clinical remission, which has persisted for over three months since the discontinuation of ACTH. Werner[154] has reported the use of ACTH in the treatment of 2 patients with thyrotoxicosis. In these patients an initial increase in basal metabolic rate

with no subsequent improvement in thyrotoxicosis, was observed. Engel[155] described a remission in a patient treated with ACTH, and Moseley and Merrill[156] observed no change in 1 case.

We have treated a patient with Graves's disease with Cortisone acetate in doses of 100 to 200 mg. daily for sixteen days.[29] A slight decrease in serum protein-bound iodine and basal metabolic rate were the only signs of improvement noted.

Adrenocortical hormones do not appear to offer any advantage over present methods of therapy in the treatment of thyrotoxicosis.

Malignant Exophthalmos

The administration of 40 to 80 mg. of ACTH for fourteen to nineteen days appeared to induce a slight improvement in 4 patients with malignant exophthalmos. The improvement consisted chiefly of a moderate relief of chemosis, lacrimation, conjunctival injection and pain, with little or no measurable effect on the exophthalmos.[28, 29] A similar patient had a decrease in periorbital edema, without other effects on the exophthalmos.[155] Koepf[157] has observed a marked exacerbation of severe malignant exophthalmos after withdrawal of ACTH therapy.

The therapy available today for malignant exophthalmos is often so ineffective that one may be justified in trying ACTH or Cortisone in the hope of effecting some partial relief of the disease by pituitary TSH suppression or by a direct effect on the orbital tissues.

Glomerulonephritis

Acute. In both of Farnsworth's[123] ACTH-treated patients there was a rapid decrease in blood urea nitrogen and cholesterol and prompt clinical recovery. The duration of symptoms prior to treatment was several weeks in both cases. One of the patients showed an initial rise in blood pressure followed by a fall to normal limits in the course of treatment. Apparently, in both patients some degree of albuminuria, hypertension and cholesterolemia remained. The doses used were 30 to 50 mg. daily in three courses of five, nine and approximately twenty-six days in a twelve-year-old girl, and 40 to 50 mg. daily in two courses of twelve and twenty days in a five-year-old girl.

We have treated 4 cases of acute nephritis with ACTH for periods varying between five and eighteen days. The duration of symptoms prior to the initiation of treatment was three days, ten days, three weeks and seven weeks respectively. In 3 cases the quantities used were 80 to 100 mg. daily in divided doses. In 1 case, that of a nine-year-old boy, 40 mg. was given every day for four days. In none of the cases was there any significant change that could be attributed directly to ACTH.

It appears from these limited observations that ACTH does not alter significantly the natural course of acute nephritis. In a disease in which the majority of cases improve spontaneously and rapidly, it is evident that a large, controlled series will be required for proper evaluation of the therapeutic action of ACTH or Cortisone.

Chronic. We have had experience with 9 cases of chronic glomerulonephritis without significant clinical edema, in 5 of which ACTH was given in doses ranging from 80 to 100 mg. per day for periods varying from four to twenty-six days, and in 4 of which Cortisone was given in doses varying from 100 to 200 mg. per day for periods varying from three to fourteen days. The disease had been present from one and a half to five years. In all cases the results were disappointing. The urinary sediment, followed daily with Addis counts, showed no consistent changes. In 5 of the 9 cases (3 on Cortisone and 2 on ACTH) there was a significant rise in twenty-four-hour urinary protein excretion during the administration of the drugs. A modest diuresis was noted in 2 of the Cortisone-treated patients after the end of treatment; no diuresis took place in the other cases. The blood urea nitrogen rose during therapy in 2 of the cases treated with ACTH and in 1 of those treated with Cortisone. The blood pressure was increased appreciably in 2 patients.

It appears that ACTH and Cortisone have little place at present in the treatment of chronic glomerulonephritis, except in the presence of definite edema, when the drugs may be helpful in inducing a diuresis in patients with the nephrotic syndrome.

Cancer

Pearson and his associates have reported the use of ACTH and Cortisone in 2 cases of carcinoma of the breast and 1 case each of carcinoma of the prostate,[119] Ewing's tumor, embryonal tumor of the testes or adrenal gland, plasma-cell myeloma, rhabdomyosarcoma and carcinoma of the pancreas.[116] No dosage schedule was given. ACTH and Cortisone therapy did not appear to affect the tumor growth in any case. Taylor and Morris,[158] on the other hand, in a preliminary communication, report a definite effect of ACTH in a few cases of malignant tumors. For instance, in a sixty-year-old man with a carcinoma of the trachea, ACTH in doses of 100 to 150 mg. daily for approximately fifty days produced marked alleviation of respiratory obstruction and healing at the site of the lesion. In a sixteen-year-old boy with Ewing's tumor given a similar dosage of the drug, there was a remission of the fever, diminution in the pain, some reduction in the local necrosis, freedom from nausea and vomiting. Similar improvement was observed in a case of mycosis fungoides and in a case of carcinoma of the breast. In another case of breast carcinoma, however, the course of the disease appeared to have been accelerated.

There is some suggestive evidence that ACTH or Cortisone may increase the catabolism of neoplastic tissue over and above that of normal tissue and thus produce a regression in the growth of cancer.[116] Bartter[159] reported that ACTH produced almost complete disappearance of an external ophthalmoplegia due to tumor metastases to the right superior orbital fissure.

It appears probable that ACTH is able to reduce markedly the tissue reaction to the cancerous material and thus to affect the symptoms of the disease, although it may exert little or no beneficial effect on the carcinoma itself.

Hypertension

No consistent effects on blood pressure have been observed in normotensive subjects treated with Cortisone. Perera[21] reported a slight fall in basal blood pressure in patients with hypertensive vascular disease given 80 mg. of Cortisone daily over a period of eight days. Like Sprague et al.,[35] we have rarely observed an increase in blood pressure during the administration of ACTH to normotensive persons. On the other hand, our experience is in agreement with Perera that hypertensive patients may show a significant rise in basal blood pressure with ACTH in doses of 60 to 200 mg. daily. One of Perera's hypertensive subjects apparently showed an encephalopathy, which cleared promptly when ACTH was discontinued.[160] We have observed 3 patients with chronic nephritis and hypertension who experienced an increase in blood pressure during ACTH therapy.

Of considerable interest are the observations by Dexter et al.[161] in a normotensive adult with rheumatoid arthritis whose blood pressure rose during sixteen days' treatment with ACTH (total dosage 1600 mg.) from 114 systolic, 86 diastolic, to 180 systolic, 120 diastolic. Cardiac-catheterization studies in this patient prior to ACTH therapy revealed a normal cardiac output and normal peripheral arteriolar resistance. Repeat studies during the period of hyptertension actually showed slight diminution in cardiac output, but a 100 per cent increase in peripheral arteriolar resistance. This strongly supports the concept of a direct vasopressor effect of some adrenal steroids.

Diseases in Which ACTH and Cortisone Are of No Value

In this group are included diseases that have had a fair trial on ACTH or Cortisone and have been found to be completely unaffected. It is obvious that this list will grow by leaps and bounds during the next year, and as it stands at present it represents only a preliminary survey.

Herpes Simplex and Zoster, Varicella and Moniliasis

The ineffectiveness of ACTH in these diseases is suggested by the fact that in 2 of our patients on ACTH and in 1 on Cortisone therapy typical herpes zoster developed during treatment with these agents. A third patient, an eighteen-year-old girl, had varicella during a period of ACTH treatment for acute nephritis. Herpes simplex and moniliasis made their appearance in several patients during the period of ACTH treatment in a variety of systemic diseases.

Poliomyelitis

The effect of ACTH on poliomyelitis has been evaluated in 35 patients as compared to a similar untreated control group by Coriell et al.[162] ACTH was administered in doses of 5 to 30 mg. every six hours for four or five days. Placebos were given to the control patients. Evaluation of response was based on change in temperature, effect on paralysis, progression of paralysis and residual effects. Case analyses revealed no demonstrable differences between the ACTH-treated patients and the untreated group.

Myopathies

Muscular dystrophy. Milhorat[163] reported on the treatment of 2 patients with myotonia atrophica who were given ACTH in doses ranging from 50 to 150 mg. per day over a period of eight days. There was no objective clinical improvement, but a significant rise occurred in the excretion of creatine on the higher dosages of ACTH. Two patients with progressive muscular dystrophy of the facioscapulohumoral type were treated for eighteen days with ACTH in amounts ranging from 40 to 100 mg. per day in four divided doses. In both cases there was no improvement in muscular function, and again a marked creatinuria was observed. Randt et al.[133] also found only slight improvement in a twenty-three-year-old woman with progressive muscular dystrophy given 1800 mg. of ACTH over a period of eleven days.

In the childhood type of pseudohypertrophic progressive muscular dystrophy under our care only a slight subjective improvement in strength followed eleven days of ACTH, amounting to a total of 1400 mg. Although the spontaneous creatinuria did not increase significantly, the creatine tolerance test showed a fall from 36 to 16 per cent retention. These findings are in essential agreement with those of Tyler et al.[164]

Muscular atrophy. Two patients, 1 with amyotrophic lateral sclerosis and 1 with progressive muscular atrophy, given 200 mg. of ACTH per day for nine and ten days[135] showed moderate improvement, but a marked exacerbation in their fasciculations when the drug was discontinued. A forty-three-year-old man with progressive muscular atrophy treated by us also failed to respond favorably.

ACTH and Cortisone do not appear to benefit patients with progressive muscular dystrophy,

amyotrophic lateral sclerosis or progressive muscular atrophy.

Cystic Fibrosis of the Pancreas

It is known that in patients with Addison's disease Cortisone may induce a reduction in fecal fat content. Observations on a five-year-old boy with pancreatic deficiency suggest that the steatorrhea observed under these circumstances is not modified by a short course of adrenal hormone therapy.

Peptic Ulcer

Although definitive studies have not as yet been completed, the clinical impression appears to have been gained that ACTH administration may aggravate the symptoms of peptic ulcer.[165] Peptic ulcer has been present in several patients with systemic diseases treated with ACTH. No healing of the ulcer has been observed under these circumstances, and in several cases ulcer symptoms have been aggravated. It is known that ACTH induces an increased secretion of gastric pepsin, which might be expected to increase the symptoms of peptic ulcer.[71] However, it is also known that ACTH stimulates the gastric mucous secretion, which, if it were in excess of pepsin secretion, might modify any detrimental effects.

Sarcoidosis

A Negro with widespread, proved sarcoidosis of two years' duration and uveal involvement was treated with ACTH in a dose of 40 mg. daily for eight days. Adequate adrenocortical response was obtained. No improvement in the clinical state or in the laboratory findings was observed during this short period of treatment. The miliary involvement of the lungs and the cystic lesions of the phalangeal bones were unchanged. The sedimentation rate remained elevated; photophobia and uveitis persisted.

Diseases in Which ACTH and Cortisone May Be Detrimental

It appears that the use of ACTH is contraindicated in diabetes mellitus, congestive heart failure, hypertensive cardiovascular disease, Cushing's syndrome, acne, hirsutism, osteoporosis and osteomalacia. The same limitation is true of Cortisone, with the exception of hypertensive cardiovascular disease. In a patient with a disease susceptible to ACTH in whom there is a complicating diabetes mellitus, it is possible to offset the diabetogenic action of ACTH or Cortisone by large doses of insulin. When therapy is discontinued a sharp fall in insulin requirements may be expected on the basis of a transient adrenal insufficiency.

Congestive heart failure and hypertensive cardiovascular disease may be aggravated by ACTH treatment. In part, this appears to be due to salt and water retention and increased peripheral resistance secondary to the administration of the ACTH preparation. Cortisone has not been shown to increase blood pressure even in hypertensive patients.

In patients with acne and hirsutism these disturbances are likely to be aggravated by prolonged ACTH or Cortisone therapy. In osteoporosis and osteomalacia, it is assumed that the negative nitrogen balance created by ACTH and Cortisone therapy and the calcium and phosphorus loss may aggravate the condition unless specific factors associated with the osteoporosis are ameliorated during therapy.

Conclusions

Thomas Addison, in 1856, suggested that the adrenal cortex was essential to life, by describing a specific deficiency syndrome in man. Almost a century later the brilliant speculations of Selye first implicated the adrenal cortex in the pathogenesis of a variety of hitherto unrelated diseases. It has remained for more recent investigations, made possible by the co-operation of physicians, scientists and the pharmaceutical industry, to demonstrate the therapeutic usefulness of ACTH and adrenal steroids in some of these diseases.

The great diversity and apparent nonspecificity of the actions of adrenal steroids suggest some single fundamental action at the cellular level. Since the two most potent steroids, Cortisone and its closely related natural precursor, Compound F, are both surface-active agents, an action on cell permeability may well prove to be the common denominator of their ubiquitous effects.

Prominent in current clinical investigation is the search for compounds that may combine therapeutic effectiveness with lower cost and fewer undesirable effects than those of ACTH and Cortisone. Already some such compounds have been shown to ameliorate to some extent certain diseases susceptible to adrenal steroid therapy. However, no agent has yet been produced that approaches the therapeutic efficiency of ACTH and Cortisone.

The use of ACTH and Cortisone in hormonal substitution therapy will do much toward restoring to normal patients with specific endocrine deficiencies. More important, however, the adrenal steroids seem capable of intervening in the manifestations of hypersensitivity of body cells to bacterial and nonbacterial substances. It appears that they inhibit the altered reactions of cells that so often prove more harmful than any direct toxic effects of the sensitizing agents themselves. Diseases that are known or thought to be based on altered tissue reactivity have in the past remained largely inaccessible to therapy. Yet it is in just such diseases that adrenal steroids exert their most spectacular effects. Even though ACTH and Cortisone may

not fulfill all the therapeutic expectations to which recent enthusiasm has given rise, it is evident that they have opened a new era in medicine.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 36221

PRESENTATION OF CASE

First admission. A twenty-five-year-old woman was admitted to the hospital because of diarrhea and evidence by barium-enema examination of an area of narrowing with ulceration in the transverse colon.

The patient was well until six months before entry, when she noticed the insidious onset of diarrhea, which gradually increased to four or five liquid movements daily. The stools were yellow to brown and never bloody. There was no mucus or pus, but the stools often looked greasy and were foul smelling. The diarrhea was not continuous, and there were periods of only one bowel movement a day, one such period occurring during the month before admission. The diarrhea was not accompanied by any pain, but there was rectal urgency — a mild, crampy feeling indicating the necessity of an immediate movement. No movements had occurred at night, and the patient had never been awakened by bowel action. There had been a temperature of 99°F. but no chills. The patient had lost 10 to 15 pounds in weight over the six-month period, associated with progressive marked weakness. There had been a little nausea but no vomiting. Six weeks before entry the patient was studied in another hospital for these complaints and was found on barium-enema examination to have an area of narrowing with ulceration about 3 cm. in length in the transverse colon. This finding was again present a month later.

As a child the patient had measles, whooping cough and "swollen glands" in the neck. At the age of eighteen she had mumps. At the age of sixteen and again two years before admission she had fever of unknown origin lasting two or three weeks. She had no symptoms referable to the chest.

The patient's husband had had nonbloody diarrhea while in the Pacific during the war and had several mild episodes of diarrhea after his return to the United States.

Physical examination disclosed a thin woman who did not appear acutely ill. The heart and chest were normal. The abdomen was flat, with slight tenderness in the right lower quadrant, where there was a sense of fullness but no definite mass. There was no spasm and peristalsis was normal. The liver and spleen were not palpable.

The temperature was 98.6°F., the pulse 88, and the respirations 20. The blood pressure was 98 systolic, 60 diastolic.

The urine was normal. Examination of the blood showed a red-cell count of 4,600,000, with a hemoglobin of 9.0 gm., and a white-cell count of 8800, with a normal differential. A blood Hinton test was negative. A stool specimen was negative for cysts, pathogens and blood. A roentgenogram of the chest showed linear areas of increased density extending upward from the upper pole of the right hilus into the right apex, where there were numerous mottled areas of increased density extending as far inferiorly as the second rib anteriorly. The findings were similar on the left but to a much lesser degree. Elsewhere the lung fields were clear. A barium enema revealed the presence of a constant area of narrowing 2 cm. in length at approximately the midtransverse colon. The margins of the area of narrowing were not shelf-like, and the mucosal pattern was normal. There was no rigidity at the site and no significant hesitation of flow of barium through the area. The cecum filled out to a normal contour, and on the post-evacuation film the lumen of the appendix was partially filled. The remainder of the bowel was not remarkable.

In the hospital the patient continued to have irregular diarrhea — up to five nonbloody stools a day. Proctoscopic examination for 15 cm. showed the mucosa to be covered with a little glairy mucus and was otherwise negative. A therapeutic test with Carbarsone and Emetine was given without success, and several stools were negative for cysts. Two sputum and gastric-aspiration examinations were negative for tubercle bacilli. On the twenty-fourth hospital day an exploratory operation was performed. In the terminal 4 feet of ileum and in the transverse colon a number of inflammatory lesions were found. These were edematous and covered with small blood vessels and contained fat growing up from the mesenteric border. The ileum was transected at a level above the lesions, except for one small lesion much higher, which if included in the resection would have required defunctioning too much small bowel. The terminal end of the small bowel was sutured in an end-to-side fashion with transverse colon distal to the lesion in the transverse colon. Examination of the other abdominal organs was negative. The postoperative

course was uneventful and the patient was discharged eleven days following operation to be followed in the Out Patient Clinic.

Second admission (thirty-one months later). In the interval the patient had gained weight and had been free of diarrhea. In addition she had had two children. For five months before admission she had three or four loose bowel movements once or twice a week and noticed progressive weakness and weight loss. Five days before entry she noted the onset of abdominal pain simultaneous with the onset of menstruation. The pain was intermittent and cramp-like and located in the right paraumbilical region. There was residual tenderness and steady pain between cramps. There was some nausea but no vomiting, and the appetite was normal. The temperature was 102°F.

On physical examination the patient appeared somewhat underweight but was in no apparent distress. The heart and lungs were normal. The abdomen was flat and soft except for the right lower quadrant, where there was a tender, ill defined mass measuring about 6 by 2 cm. Peristalsis was increased but of normal pitch. Rectal examination was negative.

The temperature was 99°F., the pulse 84, and the respirations 20. The blood pressure was 92 systolic, 60 diastolic.

The urine was normal except for occasional white blood cells in the sediment. The blood hemoglobin was 10 gm. and the white-cell count 5100, with 72 per cent neutrophils. The total protein was 6.9 gm. and the nonprotein nitrogen 16 mg. per 100 cc., the chloride 101 milliequiv. per liter and the prothrombin time 24 seconds (normal, 17 seconds). A roentgenogram of the chest showed no appreciable changes from the previous films. A plain film of the abdomen demonstrated loops of gas-filled small bowel in the left upper quadrant. Large-bowel gas was identified extending from the rectum to the midtransverse colon. In the right lower quadrant there were shadows that suggested fluid-filled loops and a minimal amount of small-bowel gas.

In the hospital the patient continued to have abdominal pain. The temperature curve was irregular, with spikes to 100°F. A barium enema was unsuccessful. On the seventh hospital day the temperature rose to 101°F., and right-lower-quadrant pain became more marked. On examination there was point tenderness just medial to and above the right anterior iliac spine. There was no spasm, and peristalsis was normal. On the following morning the temperature was 103°F., and the pulse 100. Tenderness was more marked, and spasm was present. The white-cell count was 8400. During the following three days there was some decrease in local tenderness, but the mass became larger, occupying most of the right lower quadrant. Two days later the mass presented in the right lower quadrant.

On the following day an operation was performed.

Differential Diagnosis

Dr. Horatio Rogers*: This story divides itself into two parts: first, a six-month period of painless, nonbloody diarrhea starting insidiously, accompanied by weakness and loss of weight and culminating in a surgical operation that cured the symptoms for twenty-six months; and secondly, after two years of good health, a return of the old symptoms for five months, followed by an acute episode beginning with abdominal pain five days before admission and progressing to the formation of a right-lower-quadrant mass that necessitated an abdominal operation on the thirteenth hospital day, or about eighteen days after the onset of the acute episode.

Assuming that a single disease can explain the whole three-year story, two main questions present themselves: What was the disease characterized by chronic, painless diarrhea, weakness and weight loss that responded to sidetracking of a 4-foot segment of terminal ileum only to recur two years later? Secondly, what was the nature of the acute episode leading up to the second operation?

At this point I think we might look at the x-ray films.

Dr. James J. McCort: The chest films taken at the time of the first admission show coarse strands of increased density in the apical segment of both upper lobes. These changes are more marked on the right side. There are also a few nodules and a faint suggestion of punctate calcifications at the apices, more marked on the right side. The remaining portions of the lungs are clear, and the heart and vessels are normal.

Dr. Rogers: Is it fair to ask if these changes are consistent with active tuberculosis?

Dr. McCort: They are consistent with a chronic tuberculosis. I think it is unlikely to be active; there is no evidence of cavitation. But one cannot rule out activity on the basis of the appearance of the chest roentgenogram.

On barium examination of the colon at the first admission an area of constriction, 3 cm. in length, is present in the transverse colon slightly to the left of the midline. There may be ulceration within the constricted segment, since normal mucosal folds are not seen within it. The margins of the defect in the transverse colon are not shelf-like.

The chest film taken two and a half years after the first admission shows no significant change, and this is against activity of the pulmonary process. The plain film of the abdomen made shortly after admission shows gas present in the colon extending from the midportion of the transverse colon down to the rectum. There is one dilated loop of bowel in the midabdomen that has the appearance of colon although it may be dilated ileum. There are also several other dilated loops of small bowel in the

*Visiting surgeon, Massachusetts General Hospital.

left upper quadrant. An ill defined, soft-tissue mass is present in the right lower quadrant. A definite border to this mass cannot be made out. Both kidneys are of normal size and smooth in contour. The psoas muscles are symmetrical and smooth in outline. The liver also has a smooth outline. A barium enema was attempted, but a large amount of feces was encountered, and the examination was not considered satisfactory. It appears that the narrowed area in the transverse colon is still present. It does not appear to have increased in size. There is a reflux of barium into a small segment of the ileum at the anastomosis.

DR. ROGERS: There is not complete obstruction in the narrowed area? The barium seems to go through to the right side?

DR. MCCORT: Although the examination cannot be considered adequate, barium did go through to the right side, and there is not complete obstruction at the anastomosis.

DR. ROGERS: As chronic diarrhea appears to be the most significant symptom, I shall consider a partial list of its causes that I hope may contain the correct one. The first is cancer of the colon. A lesion was twice seen on x-ray examination, but its latest description does not sound like cancer, nor does the clinical course. The surgeon apparently did not think it was cancer at the first operation. The second is primary pancreatic disease. The deformity of the transverse colon might be due to the proximity of a pancreatic mass, and the mention of foul-smelling fatty stools suggests pancreatic deficiency, but no pancreatic abnormality is mentioned at the first operation. The third is such causes as pellagra, sprue and Addison's disease, which would not be expected to improve following surgery, nor are the characteristic skin changes, stomatitis or stools described.

Ulcerative colitis is important at this age. The x-ray film showed a transverse colon with a mucosal pattern consistent with ulceration, but the rest of the colon was not characteristic of ulcerative colitis. There is no story of bloody stools to account for the low hemoglobin values observed, and the surgeon described most of the trouble as being in the small intestine.

Tuberculous enteritis is usually associated with advanced pulmonary tuberculosis, and if I understand the x-ray interpretation, this was not advanced or even active. Furthermore, the patient was apparently well for two years after the operation, which is not suggestive of pulmonary tuberculosis. The story of cervical adenitis in childhood and of undiagnosed fever at sixteen and at twenty-three years of age I will have to disregard as being irrelevant, though highly suggestive of tuberculosis.

Bacillary dysentery, amebic dysentery and other parasitic infestations are suggested by her husband's return from the Pacific islands with relapsing diarrhea, but no ova, segments or specific organisms were demonstrated in the stool, Carbarsone and Emetine were ineffective, and there was improvement following surgery.

Regional enteritis must be seriously considered. The age favors it, the surgical findings, even including slight involvement of the colon, are consistent with it, and a short-circuiting operation might be expected to bring about a symptomatic remission as it apparently did. No characteristic small bowel x-ray films are described, but none may have been taken. I think regional ileitis is the likeliest explanation for the events preceding the present illness.

We now come to the recent acute episode. Was this a chance occurrence such as appendicitis with perforation and abscess formation, or possibly a twisted ovarian cyst or acute pyosalpinx? I suppose it could have been, but I am committed to the assumption that one disease, presumably regional enteritis, can explain the whole picture. In trying to reconstruct this episode, it seems certain that something started rather gradually five days before entry and progressed with pain and fever but without much vomiting or leukocytosis for about eighteen days, when the patient became very ill and a tender mass filled the right lower quadrant. Was this an inflammatory mass from the beginning, or did it become one after starting as something else, perhaps an obstructed loop of bowel? The laboratory work gives very little help. The white-cell count fluctuated with the fever, but never went above 8400 even when the temperature rose to 103°F. The hemoglobin was 9 gm. at the first entry and was 10 gm. at the last admission, but at neither time had any external blood loss been demonstrated. We must explain it on the basis of a chronic sepsis and perhaps at least think of the possibility of bleeding into a closed loop of bowel.

If I visualize the anatomy correctly, the whole right colon, cecum, appendix and 4 feet of diseased ileum had been by-passed by anastomosing the proximal cut end of ileum into the transverse colon just distal to a constricted area and by closing the other cut end of ileum and dropping it back into the abdomen. Therefore, any further narrowing of the colonic lesion would completely isolate this large area of defunctioned bowel. Under these circumstances it could be expected to become progressively more painful and distended and finally perforate and form an inflammatory mass. The failure of the x-ray examination to show gas passing freely through the midtransverse colon and the rather gradual progress of the symptoms make something like this more likely than the type of simple acute perforation that is one of the recognized complications of regional ileitis.

Therefore, although this solution leaves a number of apparently irrelevant points unanswered, some one of which may prove to have an unrecognized diagnostic significance, I believe the most logical

explanation of the whole picture to be regional enteritis, chiefly in the terminal ileum but with other areas in the small bowel and one very important area in the transverse colon. Defunctioning of the terminal ileum and right colon brought two years of relief but no permanent cure. Then the intestine became obstructed, because of progression of the disease, contraction of scar tissue in its wall or edema, or all three, and this resulted in a closed loop, which progressed until the situation became so serious that operation had to be undertaken with the idea of at least draining an abscess and at most resecting a considerable segment of inflamed devitalized bowel and restoring intestinal continuity.

Clinical Diagnosis

Regional ileitis.

Dr. Rogers's Diagnosis

Regional ileitis with obstruction and abscess formation.

Anatomical Diagnoses

Regional ileitis, healing, with marked segmental narrowing.
Pericecal and periappendiceal abscess.
Tuberculosis of small-bowel segment proximal to anastomosis.
Tuberculous lymphadenitis.

Pathological Discussion

Dr. David Freiman: Since there is no one here who saw this patient, I shall give the operative findings as best I can. The surgeon found a mass in the region of the cecum. The whole defunctioned portion of ileum, ascending and transverse colon up to the ileotransverse colostomy was resected. In addition, an involved portion of the ileum or lower jejunum about 4 feet proximal to the anastomosis was removed. No evidence of other disease was noted in the abdomen.

The defunctioned portion of ileum and the mass around the cecum are shown in Figure 1. The arrows point to areas of marked constriction, and the lumen was obliterated in several areas, particularly in the region of the ileocecal valve. The areas between showed marked mural thickening. The valvulae conniventes of the mucosa were flattened out in many places, but there was no active ulceration. The cecum was surrounded by an inflammatory mass 7 cm. in diameter in which the appendix, with its tip doubled back upon itself, lay buried. The mucosa of the cecum was hemorrhagic and showed several areas of ulceration. Sections from this region demonstrated only a nonspecific acute and chronic inflammation with abscess formation. Sections through the area of involved ileum revealed thickening of the muscular coats of the wall, some atrophy of the mucosa and mild inflammatory reaction — all consistent with a healing phase of regional enteritis. The ascending portion of the colon was normal. The resected segment of small bowel proximal to the old anastomosis (not shown in Figure 1), however, disclosed a zone of narrowing with band-like ulceration, which on section demonstrated typical caseating tuberculosis involving both mucosa and muscularis. The lymph nodes isolated from this area and from the region of the cecum as well showed old caseous necrosis together with large numbers of active tubercles showing central caseation. There were no traces

Figure 1.

of tuberculosis recognizable histologically in the whole defunctioned segment; as a matter of fact, no granulomas of any sort were found. In view of those concepts, suggesting that regional enteritis may be due to lymphatic obstruction and lymphedema,* it is interesting to speculate whether blockage of lymph channels by tuberculosis was a contributing factor in this case. It is rather difficult to see how all traces of tuberculosis could have disappeared from the defunctioned segment even in the prolonged period since operation.

Dr. Gordon A. Donaldson: How often do you see a "skip area" that far away from the area of ileum?

Dr. Freiman: Such "skip areas" are uncommon but have been described. In this case, however, the clearly tuberculous proximal segment cannot be legitimately classified as such an area.

*Bockus, H. L. Present status of chronic regional or cicatrizing enteritis. *J. A. M. A.* **127**:449-456, 1945.

Case 36222

Presentation of Case

A forty-five-year-old male accountant was admitted to the hospital because of severe headaches.

Except for a controlled duodenal ulcer, the patient was well until three weeks before entry, when he noted the onset of dull frontal headaches, most marked over the left eye. These were controlled by a large number of Empirin tablets and after three days subsided spontaneously. Two weeks before admission, puffiness of both eyelids was noted. At about this time headaches recurred but were now bifrontal. The patient consulted an ophthalmologist who was said to have prescribed "drops" and sulfathiazole ointment for a "virus infection of the eyes." During the next four days, the puffiness gradually diminished, and the headache subsided. Ten days before entry the patient experienced rather severe pain in the back for twenty-four hours. The pain spread around into the right flank and right lateral upper quadrant of the abdomen and then cleared after three days. One week before admission the headache recurred and became constant and progressively more severe. Two days later he stopped work because he felt poorly and the headaches were so severe that he could not sleep. On the morning of the day of admission he was again seen by his physician, who found the patient's blood pressure to be "180" whereas five months before it had been recorded as "normal" and twenty-four hours before as "130." The patient was given two tablets of nitroglycerin and morphine, following which he had five or more bouts of vomiting, complained of weakness and was referred to this hospital.

The patient had known of no previous hypertension. For a number of years he had nocturia (one or two times), and during the three weeks before admission this had increased to four to five times but there were no other symptoms referable to the genitourinary tract. He had had no chills, fever or sweats and, up until the day of entry, no vomiting or nausea. Six years before entry following a period of epigastric distress, a roentgenogram demonstrated a duodenal ulcer. Since that time the patient had taken a modified ulcer diet and Amphojel, with loss of gastrointestinal symptoms. He had no history of recent head injury.

Physical examination revealed a thin man who, although in no acute distress, did not look well. There was no puffiness of the lids. The fundi showed slight arterial narrowing. The lungs were clear. The heart was slightly enlarged to the left; the sounds were of good quality, and no murmurs were heard. There was no costovertebral-angle tenderness, and abdominal and neurologic examinations were negative.

The temperature was 99°F., the pulse 75, and the respirations 20. The blood pressure was 195 systolic, 105 diastolic.

The urine was cloudy yellow, had a specific gravity of 1.014 and gave a ++ test for albumin, and the sediment contained 4 to 6 red blood cells and 3 or 4 white blood cells per high-power field, many hyaline, granular and colloid casts and a few questionable red-cell casts. The hemoglobin was 13.0 gm., and the white-cell count 13,600, with 85 per cent neutrophils, 5 per cent lymphocytes and 10 per cent monocytes. The white cells showed a shift to the left, with toxic granules; the red blood cells were normal. The serum nonprotein nitrogen was 29 mg., the calcium 9.4 mg., the cholesterol 265 mg., the phosphorus 3.2 mg., the phosphatase 2.4 units, the total protein 7.34 gm., the albumin 4.78 gm., and the globulin 2.56 gm. per 100 cc. (albumin-globulin ratio of 1.9). The sodium was 135.5 milliequiv., the chloride 93 milliequiv., and the potassium 4.2 milliequiv. per liter. The sedimentation rate was 1.5 mm. per minute. A stool was guaiac negative.

In the hospital the patient continued to complain of severe, pounding headaches and pain in the muscles of the neck and low back. One blood-pressure reading taken during a severe headache was 190 systolic, 110 diastolic. A throat culture taken on the day of admission was reported to have grown a moderate number of beta-hemolytic streptococci, and a culture of urine was positive for moderate numbers of colon bacilli. A lumbar puncture done on the second hospital day revealed an initial spinal-fluid pressure equivalent to 140 mm. of water and clear colorless fluid with 40 red blood cells and 1 white blood cell per cubic millimeter; the total protein was 40 mg. per 100 cc., and the gold-sol curve was negative.

On the third hospital day an electrocardiogram revealed a prolonged QT interval. On the tenth hospital day, a neurologic consultant found unequal, irregular pupils, a drooping right upper lid and a fine nystagmus on left lateral gaze. A roentgenogram of the skull showed slight prominence of the diploe. The white-cell count had dropped to 8000. On samples collected at odd intervals over a period of two hours and fifteen minutes, the phenolsulfonphthalein test was 37 per cent. The urea clearance was 30 per cent of normal. The total protein in a twenty-four-hour urine specimen, by volume 2270 cc., was 21.3 gm. per 100 cc. On the twelfth hospital day an intravenous pyelogram showed that the right kidney did not eliminate the opaque medium as promptly as the left, but no evidences of obstruction or other gross abnormalities were seen on either side. A Congo-red test showed 50 per cent retention in the serum, and the urine was negative for Congo-red visually. An electroencephalogram was normal except for some very questionably significant disturbances in the left posterofrontal and left central regions.

Clinically, the patient remained unchanged. Severe headaches persisted and were relieved only by Demerol. On the fifteenth hospital day a gastrointestinal series revealed a constant deformity of the duodenal cap, and at the point of greatest narrowing, there was a tiny accumulation of barium

suggesting a very small crater. The urine and white-cell count remained essentially unchanged. On the thirtieth hospital day the patient complained that he could not see. Examination revealed that he did not recognize light flashed over either eye and could not count fingers at a 61-cm. distance. However, the patient was well oriented and did not seem concerned about the matter. There was no ocular pain, diplopia or visual hallucinations. There was return of light perception after eight or nine hours, and of the ability to count fingers after fourteen hours. The left pupil was larger than the right, and the extraocular movements were normal. There was ptosis of the right eyelid. There was a fine horizontal nystagmus to the left unelicited with the opticokinetic drum and rough confrontation fields suggestive of a right homonymous hemianopia. The neck was slightly stiff, and the left arm reflexes were greater than the right.

On the thirty-third hospital day the patient fell out of bed and at that time was vomiting, incontinent and unresponsive. Examination revealed good strength throughout and normal but incoherent speech. The eyes moved and reacted but did not follow objects. The neck was stiff. He responded to painful stimuli by saying, "Oh, gee." Radial and biceps reflexes were absent, and tricep reflexes diminished but equal bilaterally. The abdominal and cremasteric reflexes were present, and the knee jerks equal and active. There was a positive Babinski sign on the right. The patient had a generalized, brief clonic convulsion beginning with turning of the head and eyes to the right and followed by clonus of the right hand and head turning to the left.

During the next two days the patient improved somewhat, but on the thirty-sixth hospital day he developed acute respiratory embarrassment, requiring aspiration and oxygen. He was unresponsive and incontinent. After insertion of an airway his color improved, but he remained in deep coma with a pulse rate of 150 to 170. One hour later he was still unresponsive but opened and moved his eyes slightly. The plantar reflexes were extensor. Several hours later he died.

During the entire hospitalization the urine and blood findings remained essentially unchanged, and the urinary output ranged from 850 to 3700 cc. The blood pressure remained fixed at about 190 systolic, 110 diastolic. Treatment in the hospital consisted chiefly of Crysticillin, Demerol and aspirin.

Differential Diagnosis

Dr. Earle M. Chapman*: We can go back in the past history of this forty-five-year-old man and find that he did have a duodenal ulcer, which was proved by x-ray examination. Perhaps we should look at the x-ray films first.

*Associate physician, Massachusetts General Hospital.

Dr. Joseph Hanelin: The findings are as given in the record. The examination of the chest was made at the time of admission, as were all the films that I am going to show. The lungs are clear, and the heart is not particularly enlarged. The intravenous pyelogram demonstrates somewhat diminished excretion by both kidneys, more marked on the right side. The kidneys are normal in size and position. I do not see any abnormal visceral shadow anywhere. The skull films are normal. The upper pole of the left kidney is not very well shown, but I cannot be certain that there is any mass present. A gastrointestinal series shows a deformed duodenal bulb, with only a questionably active crater. There is no obstruction.

Dr. Chapman: The next evidence points to the presence of bilateral renal disease, and it sounds as if he had had an acute type of nephritis. The findings were, I think, fairly clear for that. He had surprisingly little evidence of diminution in renal function. The phenolsulfonphthalein test was slightly diminished. He had a poor urea clearance test, but this was not due to uremia — the nonprotein nitrogen was normal.

We are left with two fundamental points to explain: the renal disease and the headaches, and the comatose state and death without clear localizing signs that I can interpret from the evidence on hand. I doubt if the neurologist did.

If this was nephritis, what was its origin? I am at a loss to explain nephritis unless he had more sulfathiazole than is indicated from the statement that sulfathiazole ointment was prescribed. He developed a flank pain ten days before entry and after he had been under treatment, so that raises the question whether or not he had a nephritis related to sulfonamide therapy. The blood chloride was low so it seems unlikely that he had the syndrome of hyperchloremia and encephalopathy described recently by Goodale and Kinney.† The rise in blood pressure is consistent with an acute nephritis. One wonders if there had been widespread vascular lesions throughout the body, as is so often recognized more commonly pathologically than clinically, in association with an acute hemorrhagic nephritis. I do not recall cerebral lesions on a vascular basis associated with this picture so that I cannot believe that he had a cerebrovascular lesion as a result of the nephritis.

My thought is that the patient may have had a brain tumor that I am unable to localize. The visual signs especially make me think it was somewhere along the optic tract or its radiations, but the signs were shifting and did not establish a point along the optic tract at which to localize such a tumor. The evidence all the way through suggests that the lesion was on the left side. The pain was

†Goodale, W. T., and Kinney, T. D., Sulfadiazine nephrosis with hyperchloremia and encephalopathy. *Ann. Int. Med.* **31**:1118, 1949.

first over the left eye, and some of these signs were more marked on the left side. However, the hemianopia, which was found on a rough test, was said to be on the right. If he had a lesion within the brain, it is curious that there was no evidence of increased spinal-fluid pressure on lumbar puncture; it is an unusual lesion that is growing and does not produce signs of increased pressure. Where could the source for this tumor have been? We know that he had pain in the right flank and that the right kidney by pyelogram did not fill or show as clearly as the left. One thinks of the possibility of a primary lesion located in the right kidney. I think it was Dr. Harvey Cushing who pointed out that the primary site of metastases in the brain that were unexplained was very often the lungs, and I think it was Dr. Cushing also who established the routine of always taking chest films of his patients with brain tumors. He frequently was rewarded by finding a carcinoma of the bronchus when the presenting sign of the disease was within the skull.

Dr. Hanelin: There was no evidence of any unusual mass in the chest. As far as the kidney outlines go, they seem to be perfectly smooth, and I do not see any obvious evidence of a renal tumor.

Dr. Chapman: I can go very little beyond this. I think this man had a duodenal ulcer that was not causing him too much trouble. I think acute nephritis was present, which may or may not have been related to sulfathiazole medication. I think he had a lesion within the brain, possibly on the left side — it may have been in an area of the left frontal lobe that was relatively silent. We know that lesions here sometimes resemble cerebellar signs produced by the involvement of the premotor cerebellar connections, which evidently this man did not have from the history. I think I am stumped to go beyond that.

There was one interesting thing mentioned concerning the electrocardiogram. I talked with Dr. Currens about this. The record says that the QT interval was prolonged, and this has been described with a deficiency of blood potassium. In evidence, the blood potassium was 4.2 milliequiv. per liter, which is the lower limit of normal. I could not explain a prolonged QT interval on a potassium of 4.2 milliequiv. Could you, Dr. Currens?

Dr. James J. Currens: No; I do not think so. Low calcium might possibly account for it.

Dr. Chapman: But he had a normal calcium — 9.4 mg. per 100 cc. I thought that this might be an effect of the adrenal glands, but the sodium of 136 milliequiv. per liter is a low normal — the normal in our hospital is now 136 to 140 milliequiv., and I cannot believe that the adrenal glands were affected.

That is the best I can do with the case. I think this is a puzzling and interesting case and one in which I think some astonishing results will be shown. I think he had a brain tumor, and I do not know its source.

Dr. Charles S. Kubik: Do you think that he had a hemianopia?

Dr. Chapman: The record does not tell us that he had a hemianopia. It just tells us that on rough confrontation test there was a suggestion of a right homonymous hemianopia. If so, then he would have had a left-sided lesion, I presume. Is that correct?

Dr. Kubik: And it would not have been in the frontal region.

Dr. Chapman: No, but subsequently he did not have the hemianopia. His vision cleared up and was normal again. Some of the evidence pointed to a left-sided and some to a right-sided lesion.

Dr. Tracy B. Mallory: A great many different people saw this patient on the ward and were all equally puzzled.

Dr. Allen G. Brailey: Does Dr. Chapman consider periarteritis nodosa?

Dr. Chapman: I had not mentioned periarteritis nodosa specifically, but I meant to include it with the diffuse vascular syndromes that are associated with renal disease. However, there was no eosinophilia, no fever and no pulmonary signs — nothing that led me to suspect perarteritis nodosa. There were none of the manifestations of the "group diseases" either.

Dr. Alfred E. Kranes: Is it necessary to postulate a space-occupying lesion in the brain? Might not so-called hypertensive encephalopathy account for most of the symptoms — the transient blindness, as well as some of the other confusing cerebral symptoms?

Dr. Chapman: I think hypertensive encephalopathy is usually associated with edema of the brain and an increase in the initial spinal-fluid pressure.

Dr. Kranes: Not always.

Dr. Chapman: I intended to include that, but the blood pressure was never that high; it was 180 to 190 systolic and previously was 130. I would not expect a man to develop hypertensive encephalopathy with a blood pressure at that level; I should think it would have to be higher.

Dr. Currens: A diastolic level of 110 does not seem high enough to warrant that.

Dr. Chapman: Of course, it would be helpful to explain it all on one basis.

Dr. Ruth E. Stauffer: I saw this patient several times on the ward. He had neurologic symptoms without significant localizing signs; later, there was episodic appearance of a demonstrable neurologic disorder. First, the patient developed visual loss, which was transient. Next, he had the convulsion followed by residual changes, which consisted of alteration in mental status and probable pyramidal-tract signs. Still later during a third incident he became comatose and developed unmistakable neurologic abnormalities, which persisted and even increased until the time of death.

Therefore, we concluded that these episodes were probably related to vascular insult.

DR. CHAPMAN: In reading the record I did not think so much of hypertensive encephalopathy because it did not state that he had a convulsion until the second lumbar puncture and almost as a terminal affair. That is not usually seen in association with hypertensive encephalopathy.

A PHYSICIAN: Was there any change in the eye grounds in the hospital?

DR. STAUFFER: I do not believe there was.

CLINICAL DIAGNOSES

Acute glomerulonephritis.
Cerebrovascular accident, ? aneurysm, basilar artery.
? Periarteritis nodosa.

DR. CHAPMAN'S DIAGNOSES

Acute hemorrhagic nephritis.
Acute hypertension.
Brain tumor, left frontal area.
? Diffuse vascular disease.
Duodenal ulcer, healed.

ANATOMICAL DIAGNOSES

Thrombosis, organized and fresh, of right renal artery (Goldblatt kidney).
Thrombosis, organized and fresh, of superior mesenteric artery.
Encephalopathy, ? hypertensive.
Hypertrophy of heart, slight.
Bronchopneumonia, slight.
Duodenal ulcer, healed.

PATHOLOGICAL DISCUSSION

DR. MALLORY: As is often the case in such a puzzling situation as this, it remains puzzling after the autopsy. I can describe several findings. I do not know how to tie them together into any specific pathologic entity. The most interesting finding and the one I am inclined to think is fundamental to most of the picture was a thrombosis of the right renal artery. At the time of autopsy the arterial lumen was completely obliterated, but it was possible to note that a portion of clot was fresh whereas another portion was old and partially organized, so that there was some degree of occlusion of the right renal artery for many days and, I believe, total occlusion only for a very short period. There was no infarction of the kidney and only very slight albuminous degeneration in the tubules, which as a matter of fact was equally marked in the kidney with a normal blood supply. The lesion is reasonably characteristic of an acute Goldblatt kidney and would be consistent with the sudden onset of hypertension less than two weeks before death.

The next gross finding was a similar thrombus, also part old and part fresh, in the superior mesenteric artery, again without any evidence of necrosis of the bowel so that the total occlusion must have been a matter of only a few hours before death. There was the scar of an old peptic ulcer. The heart weighed 400 gm., not significantly hypertrophied, which would confirm the clinical history that the hypertension was not of long duration. There was a little terminal pneumonia. The brain showed no macroscopic lesions, and there was no involvement of the major vessels at the base of the brain. It did show some peculiar changes on microscopical examination, which Dr. Kubik can tell us about.

DR. KUBIK: There was a restriction in the permission for the post-mortem examination requiring the brain to be replaced, and only a few blocks of tissue were removed. On microscopical examination there were numerous very small areas in which nerve cells were destroyed, but the most impressive finding was a reaction of the astrocytes, which were swollen and increased in number, indicating that there had been a severe disorder of some kind for at least a number of days. In some of the areas there were occasional, occluded, small arteries just above the size of arterioles. Some of the thrombi were canalized. Strangely enough there did not seem to be much disease of the small arteries that were not occluded, and the cause of the thrombosis is not at all clear.

This case is unusual and exceedingly interesting, and it is too bad that it was not possible to make a more complete examination of the brain. It may reasonably be assumed that changes like those described were present in other parts of the brain and that they accounted for the cerebral symptoms, but the nature of the vascular disease is not clear.

DR. MALLORY: A very large number of blocks of different organs and sections of various vessels were put through, and we could find nothing that could be called a specific arterial disease. There was nothing to suggest periarteritis nodosa, thromboangiitis, temporal arteritis or any of the other vascular diseases. In spite of the thrombosis of two of the major branches of the aorta, the patient had an exceptionally slight degree of atheroma, and the coronary arteries were entirely free of atheromatous plaques.

DR. KRANES: Might I ask whether the patient was examined during his period of blindness? Occasionally, one is able to observe striking arterial narrowing during the period of amaurosis.

DR. STAUFFER: He was examined carefully every few hours during that period.

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ONE HUNDRED AND SIXTY-NINTH ANNUAL MEETING

The one hundred and sixty-ninth consecutive annual meeting of the Massachusetts Medical Society, and the second of its Woman's Auxiliary, both duly recorded in all their details, have become part of the history of Massachusetts medicine, an attendance of 2591 at the Society and 256 at the Auxiliary meeting breaking all previous records.

The first serious business of the convocation was the stated meeting of the Council held on the evening of May 15, following the traditional Cotting supper. Probably the most important business transacted on this occasion was the reallocation, to the office of information and education, of the $8000 that has customarily been returned to the district societies from the dues paid by the fellows to the state treasury. This decision, made by an overwhelming majority of the Council, after full discussion, showed a high appreciation of the urgent need for sound organized efforts in the direction of improved public relations.

The absurdity of such a haphazard method of financing the district societies as an unpredictable kickback also became apparent to many councilors.

Further business transacted by the Council was the acceptance of the recommendation by the Committee on Ethics and Discipline that grievance committees be not organized on the district level, and that the Committee on Ethics and Discipline remain as the one committee of the Society to which complaints regarding the relations of individual fellows with the public should be referred.

The presentation by an anonymous donor of $500 to establish a "Graduation Gift Fund" was announced by the Committee on Medical Education. This fund is for the purpose of giving an annual prize and certificate to an outstanding student from each of the three medical schools in the Commonwealth, "who best exemplifies those intangible qualities which serve to designate him as a good physician." The Council further approved, on recommendation of this committee, the sponsoring of "one or more lectures for medical students on topics of medical ethics, malpractice, animal experimentation and medical society organization and objectives."

The Committee for the Red Cross Blood Program and that for the Regional Blood Center, reporting jointly, made two recommendations. The first was that the American Association of Blood Banks, which has asked for a resolution of approval, in the form adopted by the Texas Medical Society, be not approved; the second was that the delegates from the Massachusetts Medical Society to the American Medical Association, should be informed of the dangers of adopting the Texas resolution.

The reason for these recommendations is that the Texas Medical Society, in approving the American Association of Blood Banks, specifically disapproved the entrance of the Red Cross into blood-collecting in Texas, and further instructed the Texas delegates to the American Medical Association to introduce a similar measure in the House of Delegates at its San Francisco meeting. The Council adopted these recommendations.

The following officers were elected for the ensuing year: president, Dr. Leland S. McKittrick; president-elect, Dr. W. Richard Ohler; vice-president, Dr. Patrick J. Sullivan; secretary, Dr. H. Quimby Gallupe; treasurer, Dr. Eliot Hubbard, Jr.; assistant treasurer, Dr. Norman A. Welch; orator, Dr. Donald Munro.

The general sessions were held morning and afternoon on May 16, 17, and 18, and in the evening of May 16; many interesting and instructive papers were presented, as outlined in the program published on May 4. The annual meeting of the Society took place on the morning of May 16, at which the prizes mentioned above were awarded to Joseph Franklin, of Boston, a student at Boston University School of Medicine; Leonard W. Cronkhite, Jr., of Cambridge, a student at Harvard Medical School; and Miles Lee Perkins, Jr., of Togus, Maine, a student at Tufts College Medical School. Each student received, in addition to an engraved certificate, a volume of a limited edition published in 1919 by the students of Sir William Osler to commemorate his seventieth birthday, and a volume of papers published last year to commemorate the hundredth anniversary of his birth.

Thirty-two physicians who have been members of the Society for fifty years or more were presented with commemorative pins, several of them being present to receive the awards; the President delivered the annual message on the state of the Society, and the annual oration was delivered by Dr. John W. O'Meara, as previously announced. Having partaken of such intellectual refreshments, somewhat in the way of a preprandial dessert, the Society then adjourned for lunch.

On the following morning the meeting again convened at 11:05 a.m. to hear the Shattuck Lecture by Dr. Merrill C. Sosman.

That evening at the annual dinner Mrs. Howard F. Root, incoming president of the Woman's Auxiliary, and Dr. Norman A. Welch, newly elected president of Massachusetts Medical Service, were presented among other guests. The Society's first annual layman's award "to that citizen of the Commonwealth whose contribution to medical progress and support of public health projects deserves recognition by the medical profession" was then presented to Thomas F. Costello, editor and publisher of the *Lowell Sun*, after which Claude M. Fuess, Ph.D., Litt.D. (hon.), former headmaster of Phillips Andover Academy, delivered the address of the evening, entitled "As Others See You."

In closing these brief comments on a series of events so important to the fellowship of the Massachusetts Medical Society, the *Journal* takes the opportunity of congratulating Dr. Arthur W. Allen on the kindly, wise and gracious leadership that he has given the Society during the past year. The Society is all the more fortunate in being able to look forward with assurance to an equally able administration under the guidance of Dr. McKittrick.

CURFEW DELAYED

A COMPILATION recently completed by the National Office of Vital Statistics of the Public Health Service shows that death, if it has not taken a holiday, has momentarily at least stopped working overtime.

The crude death rate for 1948, about 10 per 1000 population, 2 per cent below the rate for 1947 and 1 per cent below the 1946 rate, was the lowest in the history of the country. With communicable disease relatively, if not absolutely, controlled, the chronic diseases of advancing age now sign the warrant for 63 out of every 100 persons dying.

The death rates from pneumonia and influenza and from tuberculosis reached new low marks of 38.7 per 100,000 population for the first two, and 30.0 per 100,000 for all forms of tuberculosis. Slight rises above previous levels were recorded for heart disease, cancer and diabetes, and slight declines for nephritis and intracranial lesions of vascular origin. The grim reaper rode less often on pneumatic tires in 1948 than in 1947, the rate for deaths due to motor-vehicle accidents having dropped from 22.8 per 100,000 to 22.1. Deaths from nonvehicular accidents also decreased from 46.6 to 45.0 in 1948.

The years of man are increasing, but unless they yield also a return in contributions and qualities that cannot be measured, the achievement is an empty one. Indeed, mortality and morbidity figures are so low that it becomes timely to pause at mid-

century and ask whether a healthy, older and vastly increased population is the only goal of medical activity.

Man has come a long way in the past 1949 years, slowly through demonology (the world, the flesh and the devil), haltingly past the medical milestones of Greek civilization (climates, constitutions and contagions) to a higher eminence from where he can see disease as a product of the same three factors, better understood to be sure, and renamed environment, host and agent. There are 96 elements in the atomic table now, but, for all that, he is still concerned with the earth, air, fire and water of Hippocrates. There are more than 96 diseases that can be cured or prevented, but, for all that, the four horsemen of the Apocalypse still ride faster than man's supersonic jet planes. They do not travel abreast, for, since the dawn of life, overeager "Death" has probably never claimed a single victim without the assistance of "War" (violence), "Famine" or "Pestilence." With "Pestilence" slowed down to a walk, "Famine" and "Warfare" will put spurs to their horses. Their methods of operation must be studied as objectively and scientifically as those of Pestilence. The lesson has been learned that it is not enough to cure diseases so that more doctors can heal more people. So, too, it is not enough to feed those who starve long enough to create a larger famine. It is not enough to win one war in order to be alive to kill the next race. All nations must develop positive goals of prevention of misery based on an understanding of health and of disease, of birth and death and of war and peace in terms of expanded study and research in the science of ecology, the "study of the relations of human populations to their environments and particularly to other forms of life."*

*Barnard, C. I. *The Rockefeller Foundation. A Review for 1948.* New York: The Rockefeller Foundation, 1949.

G P

April 1 — despite the day's implications — marked the advent on the national medical scene of *G P*, a new and important publication and the official organ of the American Academy of General Practice. *G P*, an abbreviation used also in referring to that organism so pleasantly symbiotic with general practice, the grateful patient, is made welcome by the *Journal* to the ranks of contemporary medical periodicals, now at approximately full regimental strength. In *G P* is seen a worthy colleague and perhaps a friendly rival, since many of the general practitioners of the country are already subscribers to the *New England Journal of Medicine*.

The first issue contains such representative papers as "A Cancer Finding Team," by Lowell S. Goin; "The Problem of Obscure Fever," by F. Kenneth Albrecht; "Office Pinch Grafting," by James L. Southworth; "Troubles in the Thorax and Abdomen," by Walter C. Alvarez; and "The Importance of Medical Economics," by R. B. Robins. Six editorials consider various subjects of interest — the future of general practice, book reviewing, hobbies, tarry stools, practical therapeutics and the National Conference on Cardiovascular Disease.

The journal is well illustrated, with both excellent halftones and many line cuts; two colors are occasionally used as part of the decorative motif, adding to the attractiveness of the format.

A tragic circumstance attending the launching of *G P* has been the untimely death of its original editor, Dr. F. Kenneth Albrecht, as the result of an automobile accident. The new journal has been fortunate in securing Dr. Walter C. Alvarez to succeed him.

MASSACHUSETTS PUBLIC HEALTH CONFERENCE

The fourth annual session of the Massachusetts Public Health Conference, sponsored by the Massachusetts Public Health Association, Massachusetts Department of Public Health, University of Massachusetts and New England Health Institute, will be held at the University of Massachusetts, Amherst, from June 14 to 16.

The program will consist of general and evening sessions on topics including advances in environmental sanitation, public-health goals of women, returns on money invested in public health and various phases of the problem of alcoholism. The sections of Health Officers, Food and Nutrition, Public Health Nurses, Health Education, Mater-

nal and Child Health and Sanitation will discuss subjects of interest to their respective members. At 7 p.m. on Thursday, June 15, the dinner of the Massachusetts Public Health Association will feature an address by Clarence Quimby, headmaster of Cushing Academy, on the subject "The Sixth Sense is the Sense of Humor." The Conference will close with a luncheon for New England health officers on Friday, June 16, at 1 p.m.

This session, like the ones held in former years, should prove worth while to all who attend it. The Conference offers physicians the opportunity not only of obtaining valuable information about the emotional, environmental and community aspects of disease, but also of participating in current plans for public health.

Cold water, in its proper application to disease, we most heartily approve of; but do not like to see such a valuable natural remedy made the hobby whereby any one can practise the healing art, and sometimes, too, without the knowledge of its first principles.

Boston M. & S. J., *May 29, 1850*

BOSTON MEDICAL LIBRARY

EXCERPTA MEDICA

Excerpta Medica, a comparatively new journal of abstracts, began late in 1947 and is now in its fourth year of publication. It endeavors to cover the whole field of medicine, including the basic and clinical fields and the specialties, and is published in fifteen sections. All abstracts are published in English and are done by authorities on their subjects from all over the world, from Boston to Tbilisi. They are signed by the abstracter, who assumes full responsibility for his work. The objectives of the editors are to furnish complete coverage of a subject and to provide informative abstracts. Necessarily, because of the difficulties connected with such an undertaking, the material is somewhat late in appearing in the printed form. However, this series of abstracting journals seems to be the best of its kind and with the projected cessation of the *Index Catalogue* should become increasingly more valuable. The sections may be obtained separately at various prices, or the whole series at the special price of $250 per annum. The sections are as follows:

SECTION I
Anatomy, Anthropology, Embryology and Histology

SECTION II
Physiology, Biochemistry and Pharmacology

SECTION III
Endocrinology

SECTION IV
Medical Microbiology and Hygiene

SECTION V
General Pathology and Pathological Anatomy

SECTION VI
Internal Medicine

SECTION VII
Pediatrics

SECTION VIII
Neurology and Psychiatry

SECTION IX
Surgery

SECTION X
Obstetrics and Gynecology

SECTION XI
Otology, Rhinology and Laryngology

SECTION XII
Ophthalmology

SECTION XIII
Dermatology and Venereology

SECTION XIV
Radiology

SECTION XV
Tuberculosis

The Library receives currently all sections and has the back series complete.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TRIPLE ANTIGEN AVAILABLE

The Division of Biologic Laboratories announces that it will be ready to begin general distribution of diphtheria and tetanus toxoids with pertussis vaccine on June 1. The effectiveness of combinations of two or more antigens has been amply demonstrated in recent years. For the past year the laboratory has been engaged in the preparation and testing of triple antigen and has now been licensed by the National Institutes of Health to distribute this material. Because this product is precipitated with alum, it should be given intramuscularly.

This combined antigen is considered most useful in children under five years of age. The complete immunization consists of three intramuscular injections of 0.5 cc., four weeks apart. Studies by the

laboratory on blood of children immunized in this manner shows a high level of immunity to all three components. Most authorities consider blood levels of 0.03 unit of diphtheria antitoxin and 0.1 unit of tetanus antitoxin per cubic centimeter to be protective. On this basis 100 per cent of the children tested were protected against both diseases. A titer of 1:320 is considered adequate protection against pertussis, and 87 per cent protection was obtained as shown by the bloods tested. A compilation of reports concerning reactions following injection indicates that these reactions compare very favorably with those after the administration of other biologic preparations, the various components administered singly or similar preparations of other manufacturers.

Fluid toxoids have been the overwhelming choice in Massachusetts, but it should be pointed out that the level of immunity obtained by a precipitated antigen is very much higher.

This triple antigen uses aluminum chloride as the precipitating agent. The amount employed is less than one sixth the permissible amount under the minimum requirements of the licensing authority. The incidence of so-called "sterile abscesses" or "antigenic cysts," which sometimes follow the use of such a product, has been materially reduced in recent years. The clinical trials of the Massachusetts product disclosed only one such "cyst" in 631 injections. This material should always be given intramuscularly. The one cyst reported could have been the result of a more superficial injection.

The Department of Public Health is very anxious to have this material available to Massachusetts physicians but urges them to avail themselves of the information contained in the circular enclosed with each vial.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR APRIL, 1950

Résumé

Disease	April 1950	April 1949	Seven-Year Median
Chancroid	0	5	2*
Chicken pox	1614	2485	1973
Diphtheria	19	42	18
Dog bite	1161	1258	1107
Dysentery, bacillary	7	2	2
German measles	258	1011	398
Gonorrhea	184	249	332
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	0	1*
Malaria	0	1	4
Measles	2022	3921	3921
Meningitis, meningococcal	7	2	14
Meningitis, Pfeiffer-bacillus	2	7	3
Meningitis, pneumococcal	6	2	5
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	1
Meningitis, undetermined	5	4	4
Mumps	899	1346	1346
Poliomyelitis	0	1	1
Salmonellosis	7	1	6
Scarlet fever	625	652	824
Syphilis	124	198	334
Tuberculosis, pulmonary	172	279	241
Tuberculosis, other forms	7	16	16
Typhoid fever	1	4	3
Undulant fever	3	2	3
Whooping cough	544	281	476

*Six-year median.

Comment

The only diseases notably above the seven-year median were bacillary dysentery and whooping cough.

Diseases below the seven-year median included chicken pox, German measles, measles, meningococcal meningitis, mumps and scarlet fever.

Whooping cough exceeded the seven-year median for the fourth consecutive month. This was the highest point for April since 1945, when there were 568 cases.

Chicken pox was at its lowest point for April since 1945. Measles continued at a low prevalence in spite of the fact that this is generally the peak season for the disease. The incidence of mumps was below the seven-year median for the third consecutive month. Scarlet fever continued at low prevalence, as it has all over the United States.

Geographical Distribution of Certain Diseases

Anthrax was reported from: Brookline, 1; total, 1.

Diphtheria was reported from: Boston, 16; Danvers, 1; Foxboro, 1; Salem, 1; total, 19.

Dysentery, amebic, was reported from: Boston, 1; Medford, 1; Worcester, 1; total, 3.

Dysentery, bacillary, was reported from: Waltham, 1; Worcester, 6; total, 7.

Encephalitis, infectious, was reported from: Worcester, 1; total, 1.

Infectious hepatitis was reported from: Lowell, 1; Wrentham, 1; total, 2.

Meningitis, meningococcal, was reported from: Fall River, 1; Lexington, 1; Quincy, 1; Springfield, 1; Weymouth, 2; Worcester, 1; total, 7.

Meningitis, Pfeiffer-bacillus, was reported from: Brockton, 1; Peabody, 1; total, 2.

Meningitis, pneumococcal, was reported from: Boston, 1; Lynn, 1; Pittsfield, 1; Swampscott, 1; Watertown, 1; total, 6.

Meningitis, undetermined, was reported from: Cambridge, 1; Great Barrington, 1; Hopedale, 1; South Hadley, 1; Springfield, 1; total, 5.

Salmonellosis was reported from: Arlington, 1; Brookline, 1; Hingham, 1; Lowell, 1; Waltham, 2; Westwood, 1; total, 7.

Septic sore throat was reported from: Adams, 1; Beverly, 1; Boston, 2; Easton, 1; Hull, 1; Taunton, 1; Worcester, 1; total, 8.

Trichinosis was reported from: Brockton, 1; Medford, 1; total, 2.

Typhoid fever was reported from: New Bedford, 1; total, 1.

Undulant fever was reported from: Haverhill, 1; Waltham, 1; Worcester, 1; total, 3.

CORRESPONDENCE

DEPRIVATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held April 27, it was voted to revoke the registration to practice medicine in this Commonwealth of Dr. Merrill L. Welcker of Worcester and Auburn, Massachusetts, because of ill health.

George L. Schadt, M.D., *Secretary*
Board of Registration in Medicine

State House, Boston

DIODRAST AND SKIODAN

To the Editor: My attention has been called to the fact that on the second column on page 657 of my Medical Progress article, "Neurosurgery," which appeared in the April 27 issue of the *Journal*, under the heading, "Methods of Visualization," the following sentence occurs approximately half way down in the paragraph: "Among them was Thorotrast..., 20 per cent *Diodrast*, which had to be abandoned..., and Iodopyracet, a water-soluble contrast medium that is still *sub judice*." The use of the word Diodrast is wrong. Actually, the material that was used was Skiodan. The Skiodan was employed in a 20 per cent solution and its use had to be abandoned for the reasons given. Similarly, in the next sentence "Skiodan" should be substituted for "Diodrast."

I am informed by the Winthrop-Stearns organization that the Iodopyracet used by Morales and Heiwinkel as referred

to in my paper is chemically identical with Diodrast for which they tell me the United States *Pharmacopoeia* and *New and Nonofficial Remedies* name is Iodopyracet.

Would you be kind enough to give this letter space in the *Journal* so that this mistake may be corrected?

DONALD MUNRO, M.D.

Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Normal Values in Clinical Medicine. By F. William Sunderman, M.D., Ph.D., professor of experimental medicine and clinical pathology, University of Texas Postgraduate School of Medicine, chief of the Department of Clinical Pathology and director of clinical research, M. D. Anderson Hospital for Cancer Research, Houston, Texas; and Frederick Boerner, V.M.D. 4°, cloth, 845 pp., with 237 illustrations and 413 tables. Philadelphia: W. B. Saunders Company, 1949. $14.00.

Essential Urology. By Fletcher H. Colby, M.D., chief, Urological Service, Massachusetts General Hospital, assistant clinical professor of genitourinary surgery, Harvard Medical School, and urological consultant, Lakeville State Sanatorium, Middleboro, Massachusetts. 12°, cloth, 580 pp., with 342 illustrations. Baltimore: Williams and Wilkins Company, 1950. $8.00.

NOTICES

ANNOUNCEMENTS

Dr. John L. O'Hara announces the opening of his office at 465 Main Street, Athol, for the practice of surgery.

Dr. Arthur E. Spiller announces the opening of an office in association with Dr. William T. Haley at 531 Beacon Street, Boston, for the practice of ophthalmology.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 13, at 12 noon. Dr. Francis D. Moore, Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief, Peter Bent Brigham Hospital, will speak on the subject "Surgical Aspects of Thyrotoxicosis in Elderly Patients."

All physicians are cordially invited to attend.

NEW ENGLAND DIABETES ASSOCIATION

The annual meeting of the New England Diabetes Association will be held at the Carney Hospital, Boston, on Wednesday, June 7, at 2 p.m.

The program will include the annual business meeting and the following clinical papers:

Surgery of the Lower Extremities in Diabetes. Charles A. Robinson, M.D.

The Present Status of Trace Minerals in Human Beings. Norman Welch, M.D.

Are We Treating Our Diabetic Patients Adequately? Charles W. Finnerty, M.D.

Infants of Diabetic Mothers. Sydney S. Gellis, M.D.

AMERICAN SOCIETY FOR THE STUDY OF STERILITY

The American Society for the Study of Sterility offers an annual award of $1000, known as the Ortho Award, for an outstanding contribution to the subject of infertility and sterility. Competition is open to persons in clinical practice as well as those whose work is restricted to research in the basic sciences. Essays submitted for the 1951 contest must be received not later than March 1, 1951. The Prize Essay will appear on the program of the 1951 meeting of the Society. For full particulars, address The American Society for the Study of Sterility, 20 Magnolia Terrace, Springfield, Mass.

WESTERN ASSOCIATION OF INDUSTRIAL PHYSICIANS AND SURGEONS

The annual meeting of the Western Association of Industrial Physicians and Surgeons will be held on Sunday, June 25 (the day prior to the opening of the American Medical Association convention) from 9 a.m. to 5 p.m. in the Curran Theater, 455 Geary Street, San Francisco.

PROGRAM

Tetanus Prophylaxis in Previously Immunized Persons. Rodney R. Beard, M.D.

Medical Administrative Problems in Workmen's Compensation Cases: A panel discussion.

A Rest Regime for Acute Back Sprain. Christopher Legge, M.D., and Harry W. Walker, M.D.

Psychosis, a Side Door out of Industry. Frank Tallman, M.D.

Job Placement in the Rehabilitation of Alcoholics: A panel discussion.

All members of the American Medical Association are invited to attend.

BRAZILIAN SOCIETY OF CARDIOLOGY

The sixth annual congress of the Brazilian Society of Cardiology will be held at the Hotel Quitandinha, Petropolis, E. Rio de Janeiro, Brazil, on July 3. In this meeting will be presented and discussed cardiologic scientific works and one of its principal aims is to favor a good friendship policy and understanding, among Brazilian and foreign doctors.

Further information may be obtained from the General Secretary of the Brazilian Society of Cardiology, Av. Nilo Peçanha, 38-5° andar., Rio de Janeiro-D.F.-Brazil.

(*Notices concluded on page xiii*)

Use herbs of conservative brewing,

Says Doc Wise, to avoid future ruing.

For drugs that are sound

In the Journal are found —

Not *the pharmacopeia of Ewing.*

12

NOTICES (*Concluded from page 886*)

SOCIETY MEETINGS AND CONFERENCES

JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.

JUNE 5 AND 8. Springfield Hospital. Page 848, issue of May 25.

JUNE 7. New England Diabetes Association. Page 886.

JUNE 12–14. American Neurological Association. Page 600, issue of April 13.

JUNE 13. New England Society of Anesthesiologists. Page 735, issue of May 4.

JUNE 13. South End Medical Club. Page 886.

JUNE 14–16. New England Health Institute and Massachusetts Public Health Conference. Page 768, issue of May 11.

JUNE 20, 22 AND 23. Springfield Hospital. Page 848, issue of May 25.

JUNE 22–25. American College of Chest Physicians. Page 270, issue of February 16.

JUNE 23 AND 24. International Academy of Proctology. Page 768, issue of May 11.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JUNE 24 AND 25. American Academy of Dental Medicine. Page 640, issue of April 20.

JUNE 25. Western Association of Industrial Physicians and Surgeons. Page 886.

JUNE 26–30. American Physicians Art Association. Page 428, issue of March 16.

JUNE 26–30. American Medical Association. Annual Session. San Francisco, California.

JULY 2–5. American Proctologic Society. Page 848, issue of May 25.

JULY 3. Brazilian Society of Cardiology. Page 886.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 28–SEPTEMBER 1. American Congress of Physical Medicine. Page 428, issue of March 16.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

OCTOBER 12–14. American Association of Blood Banks. Page 428, issue of March 16.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

JANUARY 31. American Academy of Orthopaedic Surgeons (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 8

FRIDAY, JUNE 9

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department. Mount Auburn Hospital, Cambridge.

MONDAY, JUNE 12

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, JUNE 13

*12:00 m. South End Medical Club. Headquarters, Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, JUNE 14

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.

*12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

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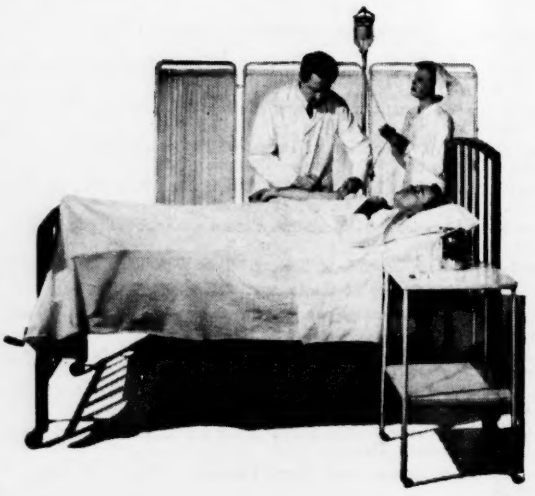

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